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By

M Reinikainen and P Pöntinen

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FROM THE CENTRAL HOSPITAL, TAMPERE FINLAND

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Preface and Object of Investigation

Numerous papers have been published concerning cardiac arrhythmias during anaesthesia and operations but they have more or less been case descriptions or related to electrocardiographic changes produced by a certain anaesthetic drug On the other hand the literature concerning these changes and especially their significance in a wider sense is rather limited so far In addition, the literature does not appear to contain any comparisons of cardiac arrhythmias in different types and during different phases of anaesthesia

For these reasons we have tried in the light of the literature available and of our own experiences to elucidate the incidence of cardiac arrhythmias during the different forms of anaesthesia and the significance of such changes

Our series consisted of 1196 patients of whom electrocardiograms were taken during anaesthesia

systoles even when the endtidal pCO is normal (48) These arrhythmias increase during inadequate respiration (35) Bradycardia is common during halothane anaesthesia, as also is the wandering pacemaker and nodal rhythm possibly resulting from increased vagal activity (2) A number of anaesthetic agents produce vagal inhibition All of the ethers cause alterations in the configuration of the P wave and forced inflation of the lungs with high concentrations of these vapours has resulted in cardiac standstill (37) Vagal inhibition has been suggested as a cause of sudden death during the induction of chloroform anaesthesia (2) As to the muscle relaxants particularly the vagal arrhythmias caused by succinylcholine are known (34 74 84)

Several types of arrhythmia occurring during anaesthesia are of atrial origin shifting of the pacemaker in the atrium or conductive disturbances in the atrioventricular node being caused by vagal irritation Although a number of authors consider the occurrence of these changes to be a sign of the onset of more dangerous arrhythmias (21, 27, 75), they are usually regarded as harmless (12, 13) A number of early authors generally regarded arrhythmias occurring during anaesthesia as interesting physiologically but clinically without significance (30, 46 51 54)

The majority of arrhythmias occurring during anaesthesia are associated with sudden changes in the tone of the autonomic nervous system and with the use of adrenaline during anaesthesia A concept has come forth that the main task of electrocardiographic monitoring during anaesthesia is to convey information of changes occurring in the autonomic nervous system (39)

Introduction

Cardiac arrhythmias are surprisingly common during anaesthesia, even when intrathoracic measures are not involved As early as 1922 Lennox et al (46) reported on the occurrence of cardiac arrhythmias during anaesthesia and operation Their series consisted of 50 patients and they stated that one half of the cases showed some abnormality of the mechanism of the heart beat Later there are great variations between different series as to the incidence, which in part may be ascribed to the monitoring technique and to the competence of the monitoring staff During the extrathoracic measures the incidences of cardiac arrhythmias vary in some series from 30 to 100 per cent (12, 25, 35, 44, 60, 71) In thoracotomies carried out under general anaesthesia, arrhythmias have been established in 77 per cent (75) On the other hand, in those performed under local anaesthesia, only axis deviations of the heart have been established (62) Heimpel (28), again has found a similar number of arrhythmias in mitral valvulotomies and in the usual extrathoracic operations during halothane anaesthesia Heart diseases remarkably increase the incidence of arrhythmias In one series, 51 4 per cent of the cardiac patients but only 19 9 per cent of other patients developed arrhythmias during anaesthesia (12) Electrocardiographic changes after a cardiac operation have been established in 40 per cent of the patients due to acidosis or anoxia, over-digitalization or operative trauma In the event of a postoperative arrhythmia, the cause should first be searched for and rectified This approach has contributed to the reduced mortality rate and decreased morbidity (61)

Arrhythmias have occurred in all possible forms of anaesthesia However, the most important proportion of them have been due to reasons other than the anaesthetic agent itself Of these causes should be mentioned reflex irritation in light anaesthesia sympathetic irritation due to hypercapnia during deep anaesthesia use of adrenaline or other sympathomimetic agents during anaesthesia, hypoxia, electrolytic disturbances, hypotension, change of intrathoracic pressure caused by manually controlled respiration etc

Several anaesthetic agents themselves cause arrhythmias Ventricular arrhythmias caused by chloroform were described by Hill already in 1932 (29) High concentrations of inspired cyclopropane will initiate ventricular extra-

small divided doses of atropine until the desired effect is obtained

Certain blood pressure controlling drugs viz. reserpine and guanethidine have been found to increase ventricular arrhythmias caused by adrenaline during halothane anaesthesia in dogs (45) According to other investigators the sensitivity to sympathomimetic amines varies according to the type of re-treatment with reserpine Supersensitivity to sympathomimetics seems to be associated with depletion of the noradrenaline stores (81)

Digitalization prior to operation may also be responsible for arrhythmias during anaesthesia

It is generally held that some common anaesthetic agents that are hydrocarbon compounds, like halothane and cyclopropane produce sensitization of the myocardium to the effects of catecholamines This must be taken into serious consideration when, for example adrenaline is used during halothane anaesthesia Under these circumstances many dangerous and even fatal arrhythmias have occurred (3 5 7, 11 26 40 63 72 75 82) In most of these cases adrenaline was infiltrated to reduce capillary bleeding Varying opinions have been advanced however and adrenaline has been recommended for use during halothane anaesthesia provided a certain dosage limit is not exceeded (23 42) In such cases arrhythmias have been easily provoked if simultaneous vagal activation is induced (59 68 69 70)

It has been established experimentally by some authors that in atrio-ventricular junctional tissue arrhythmias induced by epinephrine during cyclopropane anaesthesia were abolished by injection of acetylcholine into the left circumflex coronary artery Thiopental exerts a potentiating effect on these arrhythmias (14 15 16)

Hypoxia and especially hypercapnia play an important part in the initiation of arrhythmias Hypoxia in general does not very often cause arrhythmia in the normal heart But if the patient suffers from coronary heart disease ventricular arrhythmias are readily brought about since the excitability of the heart muscle is enhanced at the hypoxic sites (32)

In order to resolve the problems of arrhythmias during anaesthesia, the effect of extreme hypoxia and hypercapnia on the heart has been examined in experimental animals Tachycardia is first brought about by hypoxia owing to the increased sympathetic tone This is followed by bradycardia and finally by asystole

Hypercapnia also provokes ectopic rhythms It decreases the pacemaker activity Later a rapid sinus rhythm is produced again If there simultaneously prevails hypoxia conductivity is slowed down and A-V blocks of various degrees and ectopic rhythms are produced (31, 32) Acidosis occurring during high pCO_2 is regarded as responsible for the conduction disturbances thus brought about in the A-V node This may lead to a total A-V block and finally to asystole (79)

It has been established also clinically that carbon dioxide retention during halothane anaesthesia provokes various arrhythmias of ventricular origin (38) Halothane suppresses sympathetic activ-

Conditions Disposing to Abnormal Rhythm during Anaesthesia

In the previous chapter arrhythmias *caused by anaesthetic agents themselves* have been described

Atrial arrhythmias are mostly due to vagal stimulation As provoking factors may also be considered hypotension, hypoxia or advanced hypercapnia that cause inhibition of the sinus node and *activation of the lower pacemaker* situated in the region of auricles Conductive disturbances in the A-V node often are associated with vagal atrial arrhythmias Vagal activity may be so *strong that it leads to sinus arrest,* which, however, abates by itself in a well oxygenated normal heart

The most important reason for ventricular arrhythmias is the increased excitability of the ventricular muscle This is, in the first place, to be attributed to a number of drugs Sympathomimetic drugs such as adrenaline and noradrenaline give rise to arrhythmias The increase in blood pressure produces, via sinus caroticus, vagal inhibition in the sinus node but a rather small vagal effect in the conductive system of the ventricles Ventricular arrhythmias are therefore readily brought about (32) Arrhythmias have been produced with these drugs also in experimental animals and it has been established that they do not cause arrhythmia by acting on the conductive velocity but that the increased spon*taneous excitability of the fibres of the* conductive system is responsible (80)

Of the drugs used during anaesthesia, atropine in particular, because of its wide use, is responsible for a number of ventricular arrhythmias It may cause these during, for instance, halo*thane or cyclopropane anaesthesia* Because of the increased sympathetic tone due to the vagolytic effect of atropine, severe ventricular arrhythmias, even ventricular fibrillation, may *occur if ventricular extrasystoles* are present prior to administration of atropine as manifestations of sympathetic overactivity (2) These arrhythmias occur also in the presence of hypercapnia and acidosis during halothane anaesthesia or during cyclopropane anaesthesia carelessly administered Jones et al (41) state *that the* administration of intravenous atropine during cyclopropane anaesthesia may be followed by severe and dangerous arrhythmias These are *less frequent* and less severe *when the* concentration of cyclopropane is low, and their incidence is also diminished by giving

small divided doses of atropine until the desired effect is obtained

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centration of the plasma This is particularly the case when reserpine or guanethidine are administered (45) Another disease of this kind though rare is phaeochromocytoma with hypertension and a high catecholamine concentration of the plasma When anaesthesia acts as the sensitizing factor ventricular arrhythmias are readily brought about

ity and also weakens the response to hypercapnia Therefore no spontaneous arrhythmias occur in halothane anaesthesia if the cabon dioxide concentration in the blood is normal, a remarkably high carbon dioxide tension is needed to provoke them Cyclopropane, however, stimulates the sympathetic nerve and a synergism may exist between this agent and CO_2, which also leads to an increased catecholamine liberation For these reasons ventricular arrhythmias may occur in cyclopropane anaesthesia even though the endtidal pCO_2 in blood is normal The mean threshold value of the ventricular arrhythmias in cyclopropane anaesthesia has been found to be pCO_2 58 mm Hg (63) In halothane anaesthesia it was markedly higher, viz 92 mm Hg (3) In this connection the so-called posthypercapnic syndrome should be mentioned If the prolonged partial pressure of carbon dioxide, for instance *during anaesthesia, is suddenly reduced* to the normal level, dangerous arrhythmias will occur (6, 55) Thus the central effect of CO_2, with an enhanced sympathetic tone, is eliminated sooner than is the tissue acidosis with its vasodilative effect The blood pressure suddenly falls and various ventricular arrhythmias occur

Electrolytic disorders, especially alterations in the potassium concentration, have an important role in contributing to arrhythmias, as is generally known

Experimentally it has been possible to produce in certain circumstances ventricular arrhythmias in cyclopropane anaesthesia by *increasing* the blood pressure (15, 17, 18, 56) Experimental animals have been protected from fatal arrhythmias by lowering the blood pressure (22, 57)

There are also other factors capable of provoking arrhythmia during anaesthesia In the first place the so-called vasovagal reflexes are to be considered These are associated with intubation, surgical manipulations *in the lungs, and* operations on the gall-bladder and stomach (32)

Most remarkable is the vasovagal oculocardiac reflex, the reflex arc of which includes both vagal and sympathetic fibres It is known to be one of the strongest reflexes affecting the heart action and cannot entirely be abolished by a deep anaesthesia Stretching of extraocular muscles and pressure on the retrobulbar tissue in particular discharge the reflex, which is regarded as positive if the rate is slowed down more than 10 beats per minute or if arrhythmia is produced (64, 73)

It has also been noticed that the increase in the intrathoracic pressure caused by positive pressure breathing and particularly alterations in this pressure during manually controlled respiration induce high resistance in the pulmonary circulation reduce the venous return and are in part responsible for anaesthetic arrhythmias (8)

It is worth mentioning that there are diseases with an initially high sympathetic tone The most important of these is thyrotoxicosis vagal irritations during anaesthesia readily producing ventricular arrhythmias because of the elevated catecholamine con-

centration of the plasma This is particularly the case when reserpine or guanethidine are administered (45) Another disease of this kind, though rare is phaeochromocytoma, with hypertension and a high catecholamine concentration of the plasma When anaesthesia acts as the sensitizing factor ventricular arrhythmias are readily brought about

Authors' Series

A. LOCAL ANAESTHESIA

Electrocardiographic monitoring was used for 111 patients during operation carried out under local anaesthesia The majority of these operations were operations for strabismus in juvenile subjects Of these patients 27 (24 %) developed arrhythmia caused mainly by the oculocardiac reflex Details are given in table 1 As to other operations performed under local anaesthesia, this anaesthesia was used for poor risk patients in whom electrocardiographic changes such as atrial fibrillation or bundle branch block that had been established prior to anaesthesia showed no alterations during operation

As the pulse rate showed alterations during infiltration of the extraocular muscles with the local anaesthetic agents, 57 patients were keenly followed during the infiltration Of these patients, 25 showed changes in ECG

Of the patients in table 1 who developed arrhythmia none had received prior to operation any drugs that could possibly cause this condition

As was mentioned above, the main cause of arrhythmias established during local anaesthesia, the majority of which were of vagal origin, was the oculocardiac reflex produced by ocular operations It was able to bring about slight arrhythmias in spite of the fact that these conscious patients were always premedicated with either atropine or scopolamine, and the painlessness of this measure was a guarantee of a successful anaesthesia As is evident from table 1 there also were cases of ventricular extrasystoles It seems very probable that emotional factors may have been a partial cause in these cases

Table 1 Cardiac Arrhythmias during Local Anaesthesia

Arrhythmia	Number of patients
Isorhythmic A-V dissociation	2
A V dissociation with interference	1
Wandering pacemaker	2
S A block	4
S A block with nodal escape beats	1
Ectopic atrial beats	3
Nodal rhythm	4
Nodal escape beats	3
Ectopic nodal beats	1
Ectopic ventricular beats	4
I degree A-V block	2
Total	27

B EPIDURAL ANAESTHESIA

Epidural anaesthesia was mainly used for major urological and gynaecological surgery (prostatectomies nephrectomies and hysterectomies) to facilitate full muscle relaxation while spontaneous respiration was maintained The local anaesthesia was 1 5—2 0 per cent prilocaine The technique was single epidural by lumbar route Metaraminol was routinely used as a pressor agent injected subcutaneously at the beginning of anaesthesia During anaesthesia metaraminol was used intravenously in fractional doses to maintain blood pressure over 90 mm of mercury

The series comprises 85 patients operated under epidural anaesthesia Special attention in this study was given to the changes during analgesia and to the blood pressure reduction accompanying it Another subject of survey was the effect on the ECG of metaraminol used as vasopressor The recovery room was the last control point Arrhythmias were present in 23 5 per cent (20 patients) and are listed in table 2

Table 2 Cardiac Arrhythmias during Epidural Anaesthesia

Arrhythmia	Before analgesia	During analgesia	After metaraminol	Recovery room
Isorhythmic A V dissociation	—	4	1*)	—
Atrial extrasystoles	1	2	1	1
Supraventricular tachycardia	—	—	1	—
Nodal rhythm	—	4)	—	—
Nodal extrasystoles	—	1	—	—
Ventricular extrasystoles	—	1	—	1
Multifocal ventricular extrasystoles (bigeminy + trigeminy)	—	2	—	—
I degree A V block	1	1	3	—
Total	2	15	6	2

) = One of these patients was given for his slight congestive heart failure digoxin 1x1 during 12 days prior to operation At the deepening of analgesia RR *decreased* from 210 to 100 mm. Hg and nodal rhythm appeared. Metaraminol increased it to 140 mm Hg and the nodal rhythm disappeared The small dose of *digoxin* hardly was responsible for the arrhythmia

) = Immediately after analgesia this patient had isorhythmic A V dissociation that was not eliminated by *metaraminol*

Although Citanest ® used in analgesia contained vasopressor addition a drop in blood pressure regularly accompanied the spread of the analgesia In this connection four patients developed isorhythmic A-V dissociation *and four* nodal rhythm Metaraminol returned the original rhythm and the blood pressure rose to the normal level *one case excepted* Atrial and ventricular

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extrasystoles disappeared after the administration of metaraminol in 4 patients out of 6

I degree A-V block appeared in 4 patients after analgesia Evidently the reason was hypotension caused by sympathetic blockade and following transient hypoxia, which temporarily may slow down the conductivity in the A-V node After administration of metaraminol it was seen that the block was abated in two patients and the PQ interval gradually changed from 0 46 sec to 0 22 sec in connection with the rise of the blood pressure Hurwitz has also observed I degree A-V block during and after surgery in the group of patients having coronary heart disease (33)

During epidural anaesthesia the pulse rate of 42 patients slowed down, 33 patients retained their former rate, and in 10 patients the frequency was increased Obviously these changes depend mainly on the extent of the sympathetic blockade

Four of the patients were digitalized preoperatively One patient received digoxin 1 × 1 during 12 days, and one patient Cedilanid ® 1 × 3 during 14 days, the other two only during 2 or 3 days The patient given digoxin developed nodal rhythm after analgesia In the patient who had received Cedilanid ® the PQ interval was prolonged to 0 48 sec during hypotension caused by analgesia, returning to 0 22 sec after metaraminol had elevated the blood pressure to normal None of the patients had been given blood pressure controlling drugs

C HALOTHANE ANAESTHESIA

Halothane is a volatile anaesthetic, chemically 2-bromo-2-chloro-1 1 1-trifluoroethane, *which was introduced* into anaesthetic practice in 1956 Its *main advantages are quick and easy* induction without excitation, recovery *is rapid and postoperative sickness* rare Plasma catecholamine levels during halothane anaesthesia are low Increased vagal tone seen as bradycardia in unpremedicated patients is typical of halothane anaesthesia Also hypotension is a common finding during halothane anaesthesia The main disadvantage is the potentially dangerous combination of halothane and adrenaline, which has been a cause of multifocal ventricular *extrasystoles after subcutaneous* injection of adrenaline during halothane *anaesthesia, as has been mentioned* above

Succinylcholine used as muscle relaxant is a depolarizing agent The onset of action is rapid and complete paralysis lasting from 4 to 6 minutes is achieved in 30—40 seconds after initial muscle fasciculations There is no significant degree of histamine liberation by succinylcholine This agent has a central vagal effect which is accentuated with repeated doses

Gallamine is a nondepolarizing muscle relaxant The onset is rapid and paralysis lasts for about 20 minutes There

is some histamine liberation although considerably less than after d-tubocurarine The administration of gallamine is invariably followed by tachycardia which seems to be due to vagal block unaccompanied by sympathetic block

Table 3 Arrhythmias during Halothane Anaesthesia

Arrhythmia	Induction	Intubation	Maintenance of anaesthesia	Oculocardiac reflex	Recovery room
Isorhythmic A V dissociation	2	17	7	32	—
A V dissociation with interference	—	2	2	3	—
A V dissociation and wandering pacemaker	—	5	—	2	—
A V dissociation with interference and wandering pacemaker	—	—	—	1	—
Wandering pacemaker	5	4	1	13	1
Supraventricular tachycardia	—	1	2	—	—
Supraventricular extrasystoles	—	—	—	2	—
Sinus arrest	—	—	—	3	—
Sinus arrest and ventricular extrasystoles	—	—	—	—	1
Sinus arrest with nodal escape beats	—	1	—	5	—
S A block	—	1	1	1	—
S A block and nodal escapes	—	1	—	—	—
Nodal rhythm	3	5	9	27	—
Nodal tachycardia	—	2	5	5	—
Nodal extrasystoles	—	—	2	6	—
Nodal rhythm and ventricular extrasystoles with bigeminy	—	—	1	1	—
Nodal rhythm and nodal extrasystoles	—	—	—	1	—
Ventricular extrasystoles	—	1	6	5	3
Ventricular extrasystole with bigeminy	—	—	38	6	1
Multifocal ventricular extrasystoles	—	—	4	—	1
Trigeminy	—	—	1	3	4
Multifocal ventricular extrasystoles with bigeminy	—	—	6	4	—
I degree A V block	—	—	—	3	—
II degree A V block	—	—	—	—	1
Ventricular tachycardia	—	—	1	—	—
Multifocal ventricular tachycardia	—	—	1	3	—
Asystole	—	—	—	2	—
Atrial fibrillation — atrial flutter — sinus rhythm	—	—	—	—	1
Total	10	40	87	128	13

During induction of anaesthesia in 164 patients 10 (6 %) showed arrhythmia during intubation of 138 patients 40 (29 %) showed arrhythmia during maintenance of anaesthesia 87 patients out of 582 had arrhythmia (13 %) During maintenance of anaesthesia 128 out of 362 patients showed arrhythmia caused by oculocardiac reflex (35 %) and in the recovery room out of 120 patients 13 (11 %) had arrhythmia.

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C HALOTHANE ANAESTHESIA

Halothane is a volatile anaesthetic, chemically 2-bromo-2-chloro-1 1 1-trifluoroethane, which was introduced into anaesthetic practice in 1956 Its main advantages are quick and easy induction without excitation, recovery is rapid and postoperative sickness rare Plasma catecholamine levels during halothane anaesthesia are low Increased vagal tone seen as bradycardia in unpremedicated patients is typical of halothane anaesthesia Also hypotension is a common finding during halothane anaesthesia The main disadvantage is the potentially dangerous combination of halothane and adrenaline, which has been a cause of multifocal ventricular extrasystoles after subcutaneous injection of adrenaline during halothane anaesthesia, as has been mentioned above

Succinylcholine used as muscle relaxant is a depolarizing agent The onset of action is rapid and complete paralysis lasting from 4 to 6 minutes is achieved in 30—40 seconds after initial muscle fasciculations There is no significant degree of histamine liberation by succinylcholine This agent has a central vagal effect which is accentuated with repeated doses

Gallamine is a nondepolarizing muscle relaxant The onset is rapid and paralysis lasts for about 20 minutes There

is some histamine liberation although considerably less than after d-tubocurarine The administration of gallamine is invariably followed by tachycardia which seems to be due to vagal block unaccompanied by sympathetic block

Table 3 Arrhythmias during Halothane Anaesthesia

Arrhythmia	Induction	Intubation	Maintenance of anaesthesia	Oculocardiac reflex	Recovery room
Isorhythmic A V dissociation	2	17	7	32	—
A V dissociation with interference	—	2	2	3	—
A V dissociation and wandering pacemaker	—	5	—	2	—
A V dissociation with interference and wandering pacemaker	—	—	—	1	—
Wandering pacemaker	5	4	1	13	1
Supraventricular tachycardia	—	1	2	—	—
Supraventricular extrasystoles	—	—	—	2	—
Sinus arrest	—	—	—	3	—
Sinus arrest and ventricular extrasystoles	—	—	—	—	1
Sinus arrest with nodal escape beats	—	1	—	5	—
S A block	—	1	1	1	—
S A block and nodal escapes	—	1	—	—	—
Nodal rhythm	3	5	9	27	—
Nodal tachycardia	—	2	5	5	—
Nodal extrasystoles	—	—	2	6	—
Nodal rhythm and ventricular extrasystoles with bigeminy	—	—	1	1	—
Nodal rhythm and nodal extrasystoles	—	—	—	1	—
Ventricular extrasystoles	—	1	6	5	3
Ventricular extrasystoles with bigeminy	—	—	38	6	1
Multifocal ventricular extrasystoles	—	—	4	—	1
Trigeminy	—	—	1	3	4
Multifocal ventricular extrasystoles with bigeminy	—	—	6	4	—
I degree A V block	—	—	—	3	—
II degree A V block	—	—	—	—	1
Ventricular tachycardia	—	—	1	—	—
Multifocal ventricular tachycardia	—	—	1	3	—
Asystole	—	—	—	2	—
Atrial fibrillation — atrial flutter — sinus rhythm	—	—	—	—	1
Total	10	40	87	128	13

During induction of anaesthesia in 164 patients 10 (6 %) showed arrhythmia, during intubation of 138 patients 40 (29 %) showed arrhythmia during maintenance of anaesthesia 87 patients out of 582 had arrhythmia (13 %) During maintenance of anaesthesia 128 out of 362 patients showed arrhythmia caused by oculocardiac reflex (35 %) and in the recovery room out of 120 patients 13 (11 %) had arrhythmia

Electrocardiographic monitoring during halothane anaesthesia was performed on 582 patients For practical reasons the induction of anaesthesia was carried out in the majority of patients (418 patients) with thiopentone and succinylcholine In 164 patients it was performed with halothane, nitrous oxide and oxygen (column 1, table 3) Out of the patients 138 were intubated with halothane and the rest with succinylcholine This group of 138 patients is included in column 2 in table 3 (the other patients are listed in table 5, columns 2 and 3) Anaesthesia was maintained with halothane in all the 582 patients of this series Out of these, 362 were ocular operations during which the effect of the oculocardiac reflex was studied during halothane anaesthesia This series of patients is detailed in column 4 of table 3 Arrhythmias discharged by the reflex were apparent in 35 per cent of the patients Relatively numerous ventricular arrhythmias were a striking feature and evidently indicated the sympathetic component in connection with this reflex (73)

In the recovery room 120 patients were under observation after halothane anaesthesia

The premedication of all the patients included either atropine or scopolamine

A noteworthy feature was the small number of arrhythmias during induction (6 %), as is seen from table 3 These were transient vagal changes Arrhythmias during intubation were also mainly of vagal origin and were observed in 29 per cent of patients

Arrhythmias that were present during the maintenance of anaesthesia in 13 per cent were of two types When thiopentone-succinylcholine induction had been used, ventricular arrhythmias were frequent during the light halothane anaesthesia following intubation Heart muscle irritability was also partly increased by the induction of controlled respiration, because it elevates the intrathoracic pressure and causes changes in the return blood flow to the heart Although the immediate effect of intubation in general was vagal, tachycardia or ventricular extrasystoles often followed intubation carried out during halothane anaesthesia Thyrotoxic patients in particular were sensitive to ventricular arrhythmias both in connection with intubation and during the excision of thyroid tissue In the above cases the cause of arrhythmia was in all probability sympathetic irritation (catecholamine effect) In these conditions the patients often have hypercapnia due to hypoventilation, and as a consequence the catecholamine concentration of the plasma is increased

The other group comprises the typical vagal arrhythmias in smooth halothane anaesthesia A considerable number of these were isorhythmic A-V dissociation and nodal rhythm

In the recovery room 120 patients were under observation The incidence of arrhythmias was 11 per cent, the majority being various ventricular extrasystoles However, a II degree A-V block was seen in a woman aged 48, who developed ventricular extrasystoles during anaesthesia but no conductive disorders Atrial fibrillation was

discovered in a 67-year-old female patient It changed spontaneously over atrial flutter to sinus rhythm

The acid-base status and partial pressure of carbon dioxide were controlled by Astrup micro-method during maintenance of smooth halothane anaesthesia The series of twenty randomly selected patients with spontaneous respiration gave the following mean results pH 7 32 pCO_2 43 5 and standard bicarbonate 20 9

D NEUROLEPTANALGESIA

Neuroleptanalgesia, introduced by de Castro and Mundeleer at the meeting of French Society of Anaesthesiologists in 1959 is based on the simultaneous use of a strong neuroleptic drug and an effective short-acting analgesic

Table 4a Arrhythmias during Neuroleptanalgesia I

Arrhythmia	Induction	Intubation	Maintenance of anaesthesia	Oculocardiac reflex
Isorhythmic A V dissociation	—	5	—	13
A V dissociation with interference	—	1	—	6
A V dissociation and wandering pacemaker	—	—	1	2
Wandering pacemaker	—	1	—	2
Wandering pacemaker and supraventricular extrasystoles	—	1	—	—
S A block	—	—	—	1
Nodal rhythm	—	—	—	7
Nodal rhythm and wandering pacemaker	—	—	—	4
Supraventricular tachycardia	—	—	—	1
Supraventricular extrasystoles	2	18	1	3
Supraventricular tachycardia and multifocal ventricular extrasystoles	—	1	—	—
Supraventricular and ventricular extrasystoles	—	4	3	—
Nodal extrasystoles	—	1	—	1
Ventricular extrasystoles	7	16	1	6
Ventricular bigeminy	1	2	1	1
Multifocal ventricular extrasystoles	—	2	1	1
Multifocal ventricular and supraventricular extrasystoles	—	1	—	—
I degree A V block	—	2	—	4
II degree A V block	—	—	—	4
Asystole followed by III degree A V block	—	1	—	—
Idioventricular rhythm	—	1	—	—
	10	57	8	56

The total number of patients was 173 and arrhythmia was present in 86 patients (some of them showed arrhythmia at more than one stage of anaesthesia)

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A V dissociation with interference	—	1	—	6
A V dissociation and wandering pacemaker	—	—	1	2
Wandering pacemaker	—	1	—	2
Wandering pacemaker and supraventricular extrasystoles	—	1	—	—
S A block	—	—	—	1
Nodal rhythm	—	—	—	7
Nodal rhythm and wandering pacemaker	—	—	—	4
Supraventricular tachycardia	—	—	—	1
Supraventricular extrasystoles	2	18	1	3
Supraventricular tachycardia and multifocal ventricular extrasystoles	—	1	—	—
Supraventricular and ventricular extrasystoles	—	4	3	—
Nodal extrasystoles	—	1	—	1
Ventricular extrasystoles	7	16	1	6
Ventricular bigeminy	1	2	1	1
Multifocal ventricular extrasystoles	—	2	1	1
Multifocal ventricular and supraventricular extrasystoles	—	1	—	—
I degree A V block	—	2	—	4
II degree A V block	—	—	—	4
Asystole followed by III degree A V block	—	1	—	—
Idioventricular rhythm	—	1	—	—
	10	57	8	56

The total number of patients was 173 and arrhythmia was present in 86 patients (some of them showed arrhythmia at more than one stage of anaesthesia)

Thus an adequate analgesia and amnesia are obtained for the time of operation and the patient is protected against injurious reflexes All the necessary reflexes revert immediately after the operation The neurolept-analgesia I (NLA I) used in our series consists of the neuroleptic agent haloperidol and the analgesic phenoperidine, and neuroleptanalgesia II (NLA II) respectively of dehydrobenzperidol and phentanyl It is known that neuroleptic drugs, especially dehydrobenzperidol, have sympathetic alpha-receptor blocking properties (19, 50) It was first held that a sufficient protection against reflex irritations was attained with these drugs (10, 58) However, a great number of arrhythmias have been observed during NLA I in patients premedicated only with haloperidol (20)

Table 4 b Arrhythmias during Neuroleptanalgesia II and Spontaneous Respiration

Arrhythmia	Induction	Intubation	Maintenance of anaesthesia	Oculocardiac reflex	Recovery room
Isorhythmic A-V dissociation	—	1	1	1	—
Wandering pacemaker	—	2	2	—	—
Sinus tachycardia	—	7	1	—	—
Supraventricular tachycardia	—	1	—	—	—
Supraventricular extrasystoles	2	1	3	1	1
Nodal extrasystoles	—	1	—	4	—
Nodal rhythm	—	1	1	2	1
Nodal tachycardia	—	—	2	1	—
S A block and nodal escapes	—	1	—	1	—
Sinus tachycardia and ventricular extrasystoles	—	2	—	—	—
Supraventricular tachycardia and ventricular extrasystoles	—	1	—	—	—
Supraventricular and ventricular extrasystoles	—	—	—	2	—
Ventricular extrasystoles	2	7	5	4	2
Multifocal ventricular extrasystoles	—	—	2	—	—
Ventricular bigeminy	—	2	—	1	—
Ventricular trigeminy	—	—	1	—	—
Nodal escapes and ventricular extrasystoles	—	1	—	1	—
Multifocal ventricular tachycardia	—	—	1	—	—
Multifocal nodal and ventricular extrasystoles and complete A-V block and ventricular escape beats	—	—	—	1	—
Asystole	—	—	—	1	—
I degree A V block	—	1	—	—	—
	4/118	29/118	19/118	20/70	4/48

The total number of patients was 118 and arrhythmia was present in 43 patients (some of them showed arrhythmia at more than one stage of anaesthesia)

Table 4c Arrhythmias during Neuroleptanalgesia II and Controlled Respiration

Arrhythmias	Induction	Intubation	Maintenance of anaesthesia	Oculocardiac reflex	Recovery room
Isorhythmic A V dissociation	—	—	1	3	—
Sinus tachycardia	—	1	—	—	—
Nodal extrasystoles	—	—	1	1	1
Nodal rhythm	—	2	2	1	1
Nodal tachycardia	—	—	—	1	—
S A block and nodal escapes	—	2	—	—	—
Nodal rhythm and wandering pacemaker	—	1	—	—	—
Supraventricular and ventricular extrasystoles	—	1	—	—	—
Ventricular extrasystoles	—	5	3	3	1
Ventricular bigeminy	—	2	—	—	—
II degree A V block	—	—	1	—	—
Supraventricular extrasystoles	1	—	1	—	1
	1/115	14/115	9/115	9/68	4/47

The total number of patients was 115 and arrhythmia was seen in 29 patients (some of them showed arrhythmia at different stages of anaesthesia)

For this reason the authors have collected the experiences in a series of 418 patients 173 of whom were subjected to NLA I and 233 to NLA II In addition in the beginning 12 patients were given NLA II without atropine premedication The patients in the NLA I group were premedicated with haloperidol and those in the NLA II group with atropine dehydrobenzperidol and phentanyl Anaesthesia was maintained with nitrous oxide-oxygen administration In addition to ECG monitoring attention was paid to the influence of premedication acid-base balance and carbon dioxide partial pressure in capillary blood and to reflex irritation during anaesthesia Arrhythmias regarded as being due to the oculocardiac reflex are detailed in a separate column in the tables 4a 4b and 4c

The importance of atropine in the premedication becomes evident from the observations that during NLA I when the patients were premedicated with haloperidol alone various arrhythmias occurred in 50 per cent and that during NLA II the 12 patients premedicated without atropine all showed arrhythmias On the other hand in the NLA II group premedicated with atropine the incidence of arrhythmias was only 31 per cent Those occurring during NLA I in the group of 173 patients are shown in detail in table 4a

The patients of the NLA II group were operated under either spontaneous or controlled respiration. Table 4b shows the arrhythmias during spontaneous respiration in 118 patients and table 4c those during controlled res-

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Table 4 b Arrhythmias during Neuroleptanalgesia II and Spontaneous Respiration

Arrhythmia	Induction	Intubation	Maintenance of anaesthesia	Oculocardiac reflex	Recovery room
Isorhythmic A-V dissociation	—	1	1	1	—
Wandering pacemaker	—	2	2	—	—
Sinus tachycardia	—	7	1	—	—
Supraventricular tachycardia	—	1	—	—	—
Supraventricular extrasystoles	2	1	3	1	1
Nodal extrasystoles	—	1	—	4	—
Nodal rhythm	—	1	1	2	1
Nodal tachycardia	—	—	2	1	—
S-A block and nodal escapes	—	1	—	1	—
Sinus tachycardia and ventricular extrasystoles	—	2	—	—	—
Supraventricular tachycardia and ventricular extrasystoles	—	1	—	—	—
Supraventricular and ventricular extrasystoles	—	—	—	2	—
Ventricular extrasystoles	2	7	5	4	2
Multifocal ventricular extrasystoles	—	—	2	—	—
Ventricular bigeminy	—	2	—	1	—
Ventricular trigeminy	—	—	1	—	—
Nodal escapes and ventricular extrasystoles	—	1	—	1	—
Multifocal ventricular tachycardia	—	—	1	—	—
Multifocal nodal and ventricular extrasystoles and complete A-V block and ventricular escape beats	—	—	—	1	—
Asystole	—	—	—	1	—
I degree A-V block	—	1	—	—	—
	4/118	29/118	19/118	20/70	4/48

The total number of patients was 118 and arrhythmia was present in 43 patients (some of them showed arrhythmia at more than one stage of anaesthesia)

Table 5 Arrhythmias during Intubation for Different Anaesthesias

Arrhythmia	Halothane	Halothane + Succinylcholine	Thiopentone + Succinylcholine	NLA I + Succinylcholine	NLA II + Succinylcholine	Thiopentone + Succinylcholine + Propranolol
Isorhythmic A V dissociation	17	4	13	5	1	—
A V dissociation with interference	2	—	1	1	—	—
A V dissociation and sinus arrest	—	1	—	—	—	—
A V dissociation and wandering pacemaker	5	—	—	—	—	—
Wandering pacemaker	4	2	4	—	2	—
Sinus tachycardia	—	1	1	—	8	—
Supraventricular tachycardia	1	—	1	—	1	—
Supraventricular extrasystoles	—	—	7	18	1	—
Sinoatrial block	1	—	6	—	—	—
Sinoatrial block with nodal escapes	1	—	1	—	3	—
Sinus arrest with nodal escapes	1	—	—	—	—	—
Nodal rhythm	5	5	5	—	3	—
Nodal tachycardia	2	—	1	—	—	—
Nodal extrasystoles	—	1	2	1	1	—
Nodal rhythm with nodal extrasystoles	—	—	1	—	—	—
Nodal rhythm and wandering pacemaker	—	—	—	—	1	—
Nodal rhythm and ventricular extrasystoles	—	—	2	—	—	—
Sinus tachycardia and ventricular extrasystoles	—	—	—	—	2	—
Supraventricular tachycardia and ventricular extrasystoles	—	—	—	1	1	—
Supraventricular and ventricular extrasystoles	—	—	—	6	1	—
Nodal and ventricular extrasystoles	—	—	—	—	1	—
Ventricular extrasystoles	1	—	5	16	12	4
Multifocal ventricular extrasystoles	—	—	3	2	—	—
Ventricular extrasystoles and bigeminy	—	—	16	2	4	2
Multifocal ventricular and supraventricular extrasystoles	—	—	—	1	—	—
Ventricular fibrillation	—	—	1	—	—	—
WPW syndrome	—	—	1	—	—	—
Asystole followed by III degree A V block	—	—	—	1	—	—
I degree A V block	—	—	—	2	1	—
Idioventricular rhythm	—	—	—	1	—	—
Total	40	14	71	57	43	6

Arrhythmias developed in 40 patients (29 %) out of the 138 patients intubated with halothane in 14 (54 %) out of the 26 intubated with halothane and succinylcholine in 71 (17 %) out of the 418 intubated with thiopentone and succinylcholine in 57 (33 %) out of the 173 intubated with NLA I and succinylcholine in 43 (18 %) out of the 233 intubated with NLA II and succinylcholine and in 6 patients (8 %) out of the 75 intubated with thiopentone succinylcholine and propranolol.

piration in 115 patients According to an earlier investigation, patients with arrhythmias exhibit no essential differences in the acid-base balance and the carbon dioxide partial pressure as compared with other patients during neuroleptanalgesia (66) The same observation was made also now It was significant that the incidence of arrhythmia was smaller during controlled respiration than during spontaneous respiration In the latter group, arrhythmias were present during maintenance of anaesthesia in 19 patients out of 118 (about 16 %), and during the oculocardiac reflex in 20 patients out of 70 (about 29 %) On the contrary, during controlled respiration arrhythmias occurred during maintenance of anaesthesia in 9 out of 115 patients (about 8 %) and during oculocardiac reflex in 9 out of 68 patients (about 13 %)

A total of 95 patients under NLA II were under control in the recovery room, 48 of them were operated during spontaneous respiration and 47 during controlled respiration Each of these groups showed arrhythmias in 4 patients All the patients operated during NLA I were ophthalmic cases and were taken immediately to the wards from the operating theatre

E INTUBATION

Since intubation is known to give rise to strong reflex irritation and thus to produce a number of ECG changes, and since it offers possibilities to compare the different anaesthetic methods, we have considered it justifiable to devote a separate section to changes during intubation The series comprises 1075 patients whose ECG was recorded during intubation The series is divided according to the anaesthesia used for intubation as follows halothane 138 patients, halothane and succinylcholine 26, thiopentone and succinylcholine 418, neuroleptanalgesia I and succinylcholine 173, neuroleptanalgesia II and succinylcholine 233, neuroleptanalgesia II and succinylcholine without atropine premedication 12, and thiopentone succinylcholine and propranolol 75 patients Atropine was also not included in the premedication of the group given neuroleptanalgesia I and succinylcholine In the other groups all the patients were premedicated with atropine or scopolamine The patients were always ventilated with oxygen prior to intubation Arrhythmias occurring when controlled respiration was started after intubation are not regarded as being caused by intubation

The results are seen in table 5 It shows the percentage of arrhythmias in the different anaesthesia groups Special attention should be given to the ventricular fibrillation occurring after thiopentone-succinylcholine induction during intubation of a female patient aged 70 who previously had atrial fibrillation, which was corrected with the DC shock (fig 1) The patient was operated a week later under epi-

that the latter series is much smaller (26 patients) than the former (138 patients), but it may be suggestive

A total of 418 patients were intubated with succinylcholine and thiopentone In these patients arrhythmias were present in 17 per cent Supplementary to the present series there was a group of 75 patients who were additionally given beta-receptor blocking agents and exhibited arrhythmia in only 8 per cent These two series are very unequal in size and therefore not comparable but they serve to indicate that beta-receptor blockers may be important as arrhythmia-inhibiting agents

The influence of the anaesthetic agent seems to be limited to its effect on the balance of the autonomic nervous system

F REFLEX ACTIVITY

Of the reflex activities during anaesthesia the ECG changes occurring in association with intubation were already described in the preceding section The stretching of different organs such as the gall-bladder stomach and hilar regions of the lungs are mostly the triggers for reflexes mainly of vagal origin In neurosurgery a number of arrhythmias have been found to occur during manipulation of certain parts of the brains One of the strongest vasovagal reflexes is the oculocardiac reflex which was discussed above (page 10) A study of this reflex offered the possibility for comparison of the different forms of anaesthesia Further an attempt was made to explain the inhibition of reflex activity by various methods Of these should be mentioned abolishing of the vagal effect with atropine or with gallamine that has a similar action as well as blocking of the reflex arc with an analgetic agent At the same time it was our intention to examine the significance of respiration as a factor contributing to the onset of reflex activity All the cases with a change in the pulse rate of more than 10 beats per minute or developing arrhythmia of any kind were regarded as abnormal reflexes (73) The reflex activities occurring during different types of anaesthesia are shown in table 6 The first column shows the percentage of arrhythmias caused by reflex activity and the second the percentage of abnormal reflexes which includes in addition to arrhythmias the changes in pulse rate

It is evident from the table that local anaesthesia adequate for the performance of a painless operation did not prevent the reflex activities visible in the electrocardiogram the incidence of abnormal reflexes being 36 per cent in this anaesthesia During general anaesthesia (halothane) they were much more frequent occurring in 68 per cent It was possible to reduce the reflex activities by adding local anaesthesia to the general anaesthesia or by giving atropine In association with

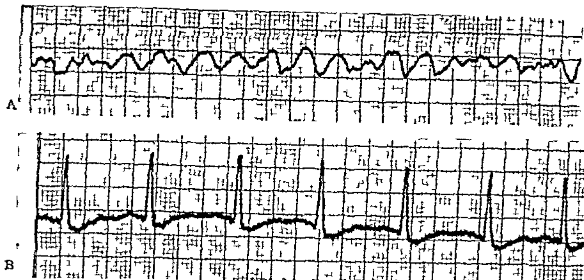


Fig 1

Ventricular fibrillation immediately after intubation during ventilation with halothane nitrous oxide and oxygen in a woman aged 70 It was terminated with DC shock (100 w s) after extrathoracic cardiac massage and oxygen ventilation (lead I)
A Ventricular fibrillation
B Sinus rhythm after DC shock

dural anaesthesia without complications but died of pulmonary embolism a week after operation

On the base of our observations it seems that arrhythmias *occur during* intubation and that they mostly are vagal but also in some instances sympathetic in origin *Atropine has* an obviously important position in the premedication as an arrhythmia-reducing factor During *NLA I*, in which it was not used, arrhythmia was present in 57 patients out of 173 (about 33 %), while in the series of *233 patients* under NLA II this agent was included in the premedication and arrhythmias occurred in *43* patients *(about 18 %)* As mentioned above, the series also consisted of a small group of patients (12 patients) in *whom the* intubation was performed during NLA II without atropine In this group there were arrhythmias mostly of atrial origin in five patients of the twelve For this reason atropine was included in the *premedication* of all the other patients intubated during this type of anaesthesia

Both the *halothane* and the halothane-succinylcholine groups consisted of children under 10 years *As is well known*, *vagal tone* is higher in children than in adults In the halothane group a number of A-V dissociations and *wandering pacemakers were seen* When succinylcholine was administered in addition to halothane a remarkably greater number of arrhythmias occurred This may have been due to the fact *that the central vagal* effect of succinylcholine enhances the similar effect of halothane It is true

that the latter series is much smaller (26 patients) than the former (138 patients), but it may be suggestive

A total of 418 patients were intubated with succinylcholine and thiopentone In these patients arrhythmias were present in 17 per cent Supplementary to the present series there was a group of 75 patients who were additionally given beta-receptor blocking agents and exhibited arrhythmia in only 8 per cent These two series are very unequal in size and therefore not comparable but they serve to indicate that beta-receptor blockers may be important as arrhythmia-inhibiting agents

The influence of the anaesthetic agent seems to be limited to its effect on the balance of the autonomic nervous system.

F REFLEX ACTIVITY

Of the reflex activities during anaesthesia the ECG changes occurring in association with intubation were already described in the preceding section The stretching of different organs such as the gall-bladder stomach and hilar regions of the lungs are mostly the triggers for reflexes mainly of vagal origin In neurosurgery a number of arrhythmias have been found to occur during manipulation of certain parts of the brains One of the strongest vasovagal reflexes is the oculocardiac reflex which was discussed above (page 10) A study of this reflex offered the possibility for comparison of the different forms of anaesthesia Further an attempt was made to explain the inhibition of reflex activity by various methods Of these should be mentioned abolishing of the vagal effect with atropine or with gallamine that has a similar action as well as blocking of the reflex arc with an analgetic agent At the same time it was our intention to examine the significance of respiration as a factor contributing to the onset of reflex activity All the cases with a change in the pulse rate of more than 10 beats per minute or developing arrhythmia of any kind were regarded as abnormal reflexes (73) The reflex activities occurring during different types of anaesthesia are shown in table 6 The first column shows the percentage of arrhythmias caused by reflex activity and the second the percentage of abnormal reflexes which includes in addition to arrhythmias the changes in pulse rate

It is evident from the table that local anaesthesia adequate for the performance of a painless operation did not prevent the reflex activities visible in the electrocardiogram the incidence of abnormal reflexes being 36 per cent in this anaesthesia During general anaesthesia (halothane) they were much more frequent occurring in 68 per cent It was possible to reduce the reflex activities by adding local anaesthesia to the general anaesthesia or by giving atropine In association with

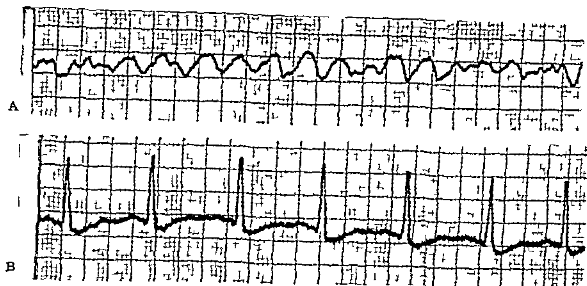


Fig 1

Ventricular fibrillation immediately after intubation during ventilation with halothane nitrous oxide and oxygen in a woman aged 70 It was terminated with DC shock (100 ws) after extrathoracic cardiac massage and oxygen ventilation (lead I)

A Ventricular fibrillation

B Sinus rhythm after DC shock

dural anaesthesia without complications but died of pulmonary embolism a week after operation

On the base of our observations it seems that arrhythmias occur during intubation and that they mostly are vagal but also in some instances sympathetic in origin Atropine has an obviously important position in the premedication as an arrhythmia-reducing factor During NLA I in which it was not used arrhythmia was present in 57 patients out of 173 (about 33 %) while in the series of 233 patients under NLA II this agent was included in the premedication and arrhythmias occurred in 43 patients (about 18 %) As mentioned above the series also consisted of a small group of patients (12 patients) in whom the intubation was performed during NLA II without atropine In this group there were arrhythmias mostly of atrial origin in five patients of the twelve For this reason atropine was included in the premedication of all the other patients intubated during this type of anaesthesia

Both the halothane and the halothane-succinylcholine groups consisted of children under 10 years As is well known vagal tone is higher in children than in adults In the halothane group a number of A-V dissociations and wandering pacemakers were seen When succinylcholine was administered in addition to halothane a remarkably greater number of arrhythmias occurred This may have been due to the fact that the central vagal effect of succinylcholine enhances the similar effect of halothane It is true

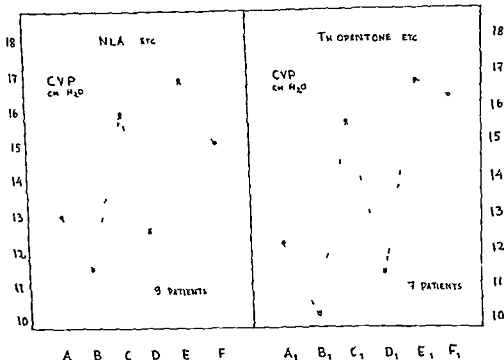


Fig 2 The mean changes in entral venous pressure (CVP) during intubation and the start of controlled respiration

A = Before anaesthesia = A B = Effect of Thalamonal® hexafluorenium and succinylcholine B = Effect of thiopentone hexafluorenium and succinylcholine C = Oxygen ventilation = C D = Intubation – D E – Oxygen ventilation E – Oxygen, nitrous oxide halothane ventilation F = 5 minutes later = F (slight decrease of CVP after 5 minutes of controlled respiration)

It is obvious that anaesthetic agents themselves seldom play an important role in the origin of arrhythmias arising soon after intubation We have come to this conclusion since after intubation the arrhythmias occurred immediately after oxygen ventilation was started and since the arrhythmias appeared in cases in which ventilation was started with oxygen nitrous oxide and halothane

The main reason for arrhythmias arising after intubation when controlled respiration is started seems to be the changes in the circulation due to elevated intrathoracic pressure In order to get a picture of the magnitude of the changes in intrathoracic pressure the central venous pressure was measured in a series of patients during and after intubation The results are presented in fig 2 This figure shows a series of 9 patients whose intubation was facilitated with Thalamonal® (= a 50 1 mixture of dehydrobenzperidol and phentanyl NLA II) hexa-

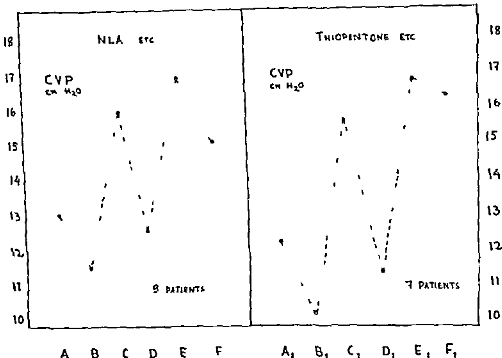
Table 6 Reflex Activities during Different Anaesthesias

Anaesthesia	Arrhythmias %	Abnormal reflexes %	Total number of patients
Local anaesthesia	22	36	101
Halothane	58	68	105
Halothane + local anaesthesia	24	43	209
Halothane + i v atropine	35	36	48
NLA I	31	45	185
NLA I + gallamine	9	13	23
NLA II + spontaneous respiration with atropine premedication	38	57	47
NLA II + spontaneous respiration without atropine premedication	58	91	12
NLA II + *controlled respiration* with atropine premedication	13	25	67
			Total 797

the latter, however, there were a comparatively large number of cases of *ventricular arrhythmia* The role of atropine in the premedication is quite clearly seen in the NLA II and spontaneous respiration groups with and without atropine premedication The former showed abnormal reflexes in 57 per cent of cases and the latter in as many as 91 per cent When controlled respiration was used in addition to atropine premedication the proportion of abnormal reflexes was reduced to 25 per cent, of which arrhythmias comprised 13 per cent Although some *asystoles of 15 to 17 seconds' duration* occurred during reflex activity, measures of resuscitation were not needed It is thus evident that even a strong vagal effect wanes by itself even though the cause of the stimulation is not eliminated The continuation of ventilation ensures and accelerates the resuming of heart action The results of animal experiments support this opinion, for in one hundred experiments carried out during controlled ventilation under various circumstances only one arrhythmia and one abnormal reflex activity were observed (64)

G OTHER FACTORS INDUCING ARRHYTHMIA DURING ANAESTHESIA

One of the most important causes of arrhythmia is carbon dioxide retention, especially when it occurs in association with hypoxia (31), as was mentioned above An example of this was an electrocardiogram recorded during bronchoscopy, showing ventricular *extrasystoles induced by hypercapnia* and hypoxia which were eliminated by *oxygen ventilation* The ventricular extrasystoles observed in the recovery room *also are often a consequence of* hypoventilation and carbon dioxide retention



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fluorenium and succinylcholine (in fig 2 NLA etc), and another series of 7 patients intubated with the aid of thiopentone, hexafluorenium and succinylcholine (in fig 2 Thiopentone etc) As is evident from figure 2, there was a marked elevation of CVP during oxygen ventilation both before and after intubation and also during oxygen, oxygen-nitrous, halothane ventilation after intubation

Thus at the onset of arrhythmias there is no reason to change the anaesthetic It may also be mentioned that the arrhythmia disappears if spontaneous respiration is reintroduced, with the halothane still on It also disappears later even if controlled respiration is continued together with halothane, for the circulatory system adapts itself gradually to the new conditions when controlled respiration is smoothly continued The arrhythmia disappears when the venous return is normalized

Relaxants may in many ways be responsible for the arrhythmias, as was mentioned above Gallamine which has a similar cardiac effect as atropine, is, like the latter, capable of inducing sympathetic arrhythmias by decreasing vagal tone One of our patients developed multifocal ventricular extrasystoles after the administration of gallamine Tachycardia is common after this drug (32) Increased vagal tone is a typical consequence of succinylcholine administration and is enhanced when the dose is repeated, as has been noticed

Discussion

In our series arrhythmias usually occurred in a number of cases during every form of anaesthesia

The most significant arrhythmias during anaesthesia are the various rapid tachycardias Cardiac arrests of various origins also deserve keen attention Among tachycardias occurring during anaesthesia special consideration should be given to ventricular tachycardia We were able to record some of them on the electrocardiogram during halothane anaesthesia (see table) Three of them were considered to be due to the oculocardiac reflex and the others were possibly provoked by hypoxia One ventricular tachycardia occurred during NLA II with spontaneous respiration and may also have been due to hypoxia Correction of ventilation and termination of reflex activity sufficed to stop the tachycardia in all these instances When these measures do not prove successful the use of beta-receptor blockers and direct current countershock should be considered After the administration of DC shock the patients may easily develop other arrhythmias (67) In such instances beta-receptor blockers should be given

Supraventricular tachycardia occurring during anaesthesia is not infrequent In our series there were seven cases In two cases we considered it a consequence of superficial anaesthesia and by deepening the anaesthesia were able to stop this arrhythmia In one instance it was thought to be due to administration of gallamine, which has an atropine-like effect In the remaining cases the tachycardia was evidently to be attributed to vasovagal reflex and the arrhythmia disappeared after termination of the reflex activity

In this series one case of ventricular fibrillation occurred during intubation (see page 20) External heart massage and oxygenation of the myocardium are advisable in such cases prior to DC shock which has proved effective also in the defibrillation of an anoxic heart (47) The simultaneous use of beta-receptor blockers is recommended in order to prevent the recurrence of ventricular fibrillation for instance an intravenous dose of 2—4 mg of propranolol In some instances merely the propranolol treatment has been successful in terminating ventricular fibrillation (76)

As was stated cardiac arrest during anaesthesia is an arrhythmia that must

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during prevailing sinus rhythm is mostly of no great harm to the circulatory system

In order to avoid arrhythmias during anaesthesia to as great an extent as possible it is important to prepare the patient carefully for the operation An essential detail in this is a preoperative visit of the anaesthesiologist to the patient for the purpose of examination and to calm the patient Adequate oxygenation provides better conditions for continuance of the pacemaker activity and for transmission of the impulse The inhibition of hypercapnia by proper attention to ventilation and carbon dioxide absorption will reduce the incidence of ventricular arrhythmias

The attainment of electrolyte balance already prior to operation especially the normalizing of the potassium concentration of the plasma is of utmost importance for the prevention of arrhythmias In particular digitalized patients and those given diuretics often reveal a lack of potassium Such patients may have to be acutely operated on because of some sudden disease requiring surgery In these patients the risk of arrhythmias due to digitalis intoxication may be prophylactically reduced with beta-receptor blockers administered during operation In this connection it may be mentioned that in our series there was a very small number of patients (about 3 to 4 %) who preoperatively received digitalis or blood pressure reducing drugs Furthermore the majority of the patients had taken these drugs only during a short time prior to operation Among these patients there naturally were acute operative cases that had been digitalized over a longer period of time However, on account of the small number of such cases these drugs can not be considered to have had any role of importance in the development of arrhythmias in our series Another circumstance in which beta-receptor blockers should be employed to inhibit arrhythmias during anaesthesia is when adrenaline is indicated during halothane anaesthesia The risks attached to the simultaneous administration of adrenaline and halothane have already been discussed in this paper Under these circumstances it obviously is safest to protect the myocardium against the effects of catecholamine with propranolol With this agent it also is possible to reduce capillary bleeding and to maintain controlled hypotension and thus to provide a possibility to infiltrate simultaneously the operative field with adrenaline (36 65)

Another agent used in our series during operation for the prevention of arrhythmias is atropine Certain vagal reflexes are so strong that the usual dose of atropine used for premedication is not adequate for their inhibition A typical reflex of this kind is the oculocardiac reflex We have administered atropine intravenously or in some cases gallamine just prior to the reflex activity Blocking of the reflex arc with a local anaesthetic has also been recommended (4 9 43 53) For subjects with a healthy cardiovascular system even a strong vagal activity is not sufficient to cause a sustained cardiac arrest and careful ventilation and

be seriously considered In this series two patients had a circulatory arrest of nearly 40 seconds' duration caused by vasovagal reflex We should like to emphasize that *in instances of cardiac* arrest metabolic acidosis quickly develops during even a short circulatory arrest, in some cases it is preceded by respiratory acidosis Its correction with sodium bicarbonate is as important as attending to the respiration and massaging the heart The literature describes a number of fatalities during strabismus operation in children with a healthy circulatory system, caused by asystole provoked by the oculocardiac reflex (1, 43, 49, 77, 78, 83) Thus it is advisable to closely observe any rhythm during reflex activity and in case of need to start the necessary treatment in time

As is seen from the presented tables, a considerable number of the arrhythmias occurring during anaesthesia were in great part due to enhanced vagal tone (atrio-ventricular dissociation, wandering pacemaker, sino-atrial block, sinus arrest, nodal rhythms, as well as a few nodal tachycardias, etc) They could also have been the consequence of hypoxia or of ischaemia and depression of the sinus node caused by deep anaesthesia Because of their short duration these arrhythmias were not significant Vagal blockade or attention to oxygenation and ventilation usually sufficed for their control

Likewise there were a great number of ventricular extrasystoles, caused either by sympathetic overactivity or by increased irritability of the myocardium The former might have been due to effective vagal blockade during anaesthesia The latter is caused by *sensitization to catecholamines induced* by certain anaesthetic agents, enhanced catecholamine concentration of plasma due to carbon dioxide retention, and, especially in patients with coronary heart disease, simultaneous hypoxia and carbon dioxide retention, as has been discussed above In some instances there was bigeminy of long duration and multifocal ventricular extrasystoles If, for some reasons, *oxygenation did not prove helpful, they* were eliminated by administration of beta-receptor blockers These agents protect the myocardium against both endogenous and exogenous increase of catecholamines, at the same time allowing time to solve the basic reason for the arrhythmia

We should like to state further that bradycardia was comparatively common during anaesthesia in our series However, these cases are not included in the tables Bradycardia is mostly a consequence of vagal overactivity caused by certain anaesthetic agents, as already was mentioned Atropine, which is generally used in the premedication, obviously is important as an antiarrhythmic agent *This became* very clear during neuroleptanalgesia In our experience atropine is not always able to completely eliminate the vagal overactivity If, in addition, vagal reflex activity, for instance the oculocardiac reflex is brought about or the vagal effect is increased by muscle relaxants (succinylcholine), a fairly intensive bradycardia may be produced However, such bradycardia

Summary

Factors causing arrhythmia during anaesthesia and operation are first discussed in general. The series comprises 1196 patients whose ECG was monitored during anaesthesia. Electrocardiograms were recorded from 111 patients during operations carried out under local anaesthesia. The majority of these measures were operations for strabismus in juvenile subjects. Arrhythmia was present in 24 per cent of the patients. The majority of these were of vagal origin caused by the oculocardiac reflex. There also were cases of ventricular extrasystoles probably caused by emotional factors. Eighty-five patients were operated under epidural anaesthesia. Arrhythmia occurred in twenty patients (23.5 %). Special attention was given to the changes during analgesia and to the blood pressure reduction accompanying it. Metaraminol abolished the abnormal rhythm from the majority of the patients (A-V dissociation, nodal rhythm, atrial and ventricular extrasystoles). Similarly I degree A-V block disappeared in two patients out of four.

Electrocardiographic monitoring during halothane anaesthesia was performed on 582 patients. The induction of anaesthesia was carried out with thiopentone and succinylcholine in most of the cases. In 164 patients it was performed with halothane, nitrous oxide and oxygen. Of the total of the patients 138 were intubated with halothane and the remaining part with succinylcholine. Of the whole series 362 cases were ophthalmic operations during which the effect of the oculocardiac reflex was studied during halothane anaesthesia. This series of patients is presented in the tables in detail. Arrhythmias discharged by the reflex were apparent in 35 per cent of the patients. Six per cent of the patients developed arrhythmias during induction. These were transient vagal changes. Arrhythmias during intubation were also mainly of vagal origin and were observed in 29 per cent of the cases.

Thirteen per cent of the patients showed arrhythmias during the maintenance of anaesthesia. They were of two types. When thiopentone-succinylcholine induction had been used, ventricular arrhythmias were frequent during halothane anaesthesia. The other group comprises the typical vagal arrhythmias in smooth halothane anaesthesia.

oxygenation are sufficient to inhibit the onset of dangerous arrhythmias

The value of electrocardiographic monitoring during anaesthesia is of great importance It reveals immediately any startling cardiac arrests The other changes in the ECG alert us to check whether changes that need to be repaired have occurred in the course of anaesthesia

It is difficult to say in advance which of the patients require ECG monitoring, although it is obvious that in aged persons and in patients with heart disease more electrocardiographic changes are to be expected during anaesthesia and operation Furthermore it is generally held that a recent myocardial infarction indicates a poor risk for anaesthesia and operation (52)

Our series contained surprisingly few patients (2—3 %) whose ECG had shown changes as a sign of coronary sclerosis This may be due to the rather great number of juvenile patients hospitalized for ophthalmic operations On the basis of the above these ECG changes cannot be regarded as important arrhythmia-causing factors in our own series

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Neuroleptanalgesia I was performed for 173 patients and neuroleptanalgesia II for 233 Atropine was not included in the premedication in the NLA I group in which various arrhythmias were present in 50 per cent of the cases On the other hand, in the NLA II group premedicated with atropine the incidence of arrhythmias was 31 per cent

The patients of the NLA II group were operated under either spontaneous or controlled respiration Arrhythmias *were present under spontaneous respiration* during maintenance of anaesthesia in 16 per cent of the cases and arrhythmias caused by the oculocardiac reflex in 29 per cent The corresponding values under controlled respiration were 8 per cent and 13 per cent

Arrhythmias during intubation are described in detail in a separate section The series comprises 1075 patients and is divided according to the anaesthesia used for intubation Arrhythmias that occurred were mainly vagal but also in some instances sympathetic Atropine has an obviously important position in the premedication as an arrhythmia-reducing factor

The effect of oculocardiac reflex was *examined in different forms of anaesthesia* In addition, attention was paid to other factors provoking arrhythmias, such as the significance of pCO_2, central venous pressure as well as muscle relaxants

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SUPPLEMENTUM 456

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BY

TIMO SOMER

ACCOMPANIES VOL. 180

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ACKNOWLEDGEMENTS

The present study was carried out in 1961—1965 at the Wihuri Research Institute Helsinki The theme was suggested by my esteemed teacher, Professor Pentti I Halonen M D, head of the Wihuri Research Institute and of the First Department of Medicine University of Helsinki It is a pleasure for me to express my deep gratitude to Professor Halonen for placing the laboratory facilities of the Institute at my disposal and for his keen interest, encouragement and valuable criticism during all stages of the work

I also extend my thanks to Professors I Vartiainen M D and E. A Nikkila M.D heads of the Second and Third Departments of Medicine University of Helsinki and to Professor P Brummer M D head of the Medical Clinic University of Turku, for their kind permission to obtain the necessary samples from the patients hospitalized in the departments under their direction Professor Nikkila moreover gave valuable suggestions during the initial planning of the manuscript

I am greatly indebted to Docent V Laine M D head of the Rheumatism Foundation Hospital Heinola for his helpful attitude in the collection of the blood samples from patients in his hospital and for his interest and advice Professors C A Hernberg M D, E. Klemola, M D, and M Virkkunen, M D, and Docent S G Jokipii, M D, also kindly provided samples from the patients under their care

With the generous assent of Docent H R Nevanlinna M D, the serum immunoelectrophoretic analyses were performed at the Central Laboratory of the Finnish Red Cross Blood Transfusion Service Helsinki The analyses were expertly interpreted by Dr P Vuopio, M.D The serum ultracentrifugal analyses were kindly carried out by Mr R Schakir M S (Chem Eng) at the State Serum Institute Helsinki To all of them I extend my best thanks.

I also wish to convey my thanks to Associate Professor P I Branemark M.D Department of Anatomy, University of Gothenburg Sweden to Dr L. Dintenfass Ph. D Sydney, Australia and to Professor L. E. Gelin M D, head of the Department of Surgery I, Sahlgrenska Sjukhuset Gothenburg Sweden for profitable discussions during an interesting meeting in Gothenburg in 1965

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Helsinki, May 1966

Timo Somer

INTRODUCTION

One of the most characteristic features of multiple myeloma and Waldenstrom's macroglobulinemia is the abundant production of abnormal serum proteins These paraproteins are rather generally thought to contribute more or less directly to some of the symptoms in these diseases Although the relationship between the elevated serum or blood viscosity in consequence of the excess of paraproteins and the ensuing clinical manifestations in malignant reticuloses has been recognized for years amazingly few studies have been made with the primary goal to observe the interrelations of paraproteins and viscosity *in vitro* With few exceptions such studies on the viscosity of blood plasma and serum have included only a few patients and have been performed with very heterogeneous viscometric methods Moreover the solitary cases and small series of patients reported thus far have often represented extreme qualitative and quantitative protein changes with striking clinical manifestations Hence, the concepts of serum, plasma and blood viscosity levels which are influenced also by methodical factors, may be somewhat misleading Likewise, the effects of the specific physicochemical properties of paraproteins, which may be pathogenetically as decisive as their concentrations have not been sufficiently correlated to viscosity

In view of the above observations it was felt to be worth while to study the levels of the viscosity of blood, plasma and serum with a uniform technique A comparison of viscosity data with protein alterations and molecular properties as they manifest themselves by clinically used methods was also included in order to assess the applicability of viscometry as a laboratory tool

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In view of the above observations it was felt to be worth while to study the levels of the viscosity of blood, plasma and serum with a uniform technique. A comparison of viscosity data with protein alterations and molecular properties as they manifest themselves by clinically used methods was also included in order to assess the applicability of viscometry as a laboratory tool.

nificance are non Newtonian, i e, they do not obey the law of Poiseuille In Newtonian (»ideal) fluids (e g water) the rate of flow is proportional to the pressure (shear stress) causing it Thus they have a definite coefficient of viscosity (η) and the same »apparent viscosity» independent of the conditions of measurement Due to its departure from Poiseuille's law and to its variable viscosity the viscosity of blood has been often called »anomalous»

Nature of viscosity of blood — The first hints of the non Newtonian nature of blood seem to come from the studies of Ewald (1877) du Pre'Denning & Watson (1906) and Hess (1907) Since then, many workers (reviewed by e g Bayliss 1952 1960 and Dreizen 1962) have confirmed the result that the apparent viscosity of blood varies, because of its multiform composition (a suspension of cells chylomicrons, carbohydrates proteins electrolytes etc in an aqueous medium) according to the circumstances in which the flow takes place In other words, the viscosity of blood and other non Newtonian fluids is highly shear dependent in particular so that the apparent viscosity increases at low rates of flow and is reduced with increased shear stress and rate of shear

Methods of investigation in rheology and viscometry

As a consequence of what has been stated it is evident that the choice of experimental techniques in hemorheology is essential in relation to results These methodical questions have been recently discussed among others by Bloch (1962 1963) and especially by Wayland (1965 b), who concluded by stating »there is no best method of studying the rheological properties of blood» In addition, hemorheology has during the past few years made progress especially in methodical advancements with a speed in consequence of which tools and techniques usually become somewhat out of date in the scientific sense within a brief time

In principle in order to obtain characteristic factors of blood flow properties the study should be conducted in a part of the living intact organism that represents a typical area of the microvascular compartment and in a way that permits some quantitative and comparable determinations of flow parameters There is at present no relevant method which really describes the actual microcirculatory *events* as to particular parameters al*though* future progress seems to aim also at quantitative *in vivo determinations* for instance of viscosity These *in vivo* aspects of blood rheology have been discussed by Branemark (1964) Harders (1964 1965) Wayland (1965 b), Wells (1964), and others

Reliable quantitative information on the flow properties of blood and plasma can thus be obtained at present only by *measurements in vitro* Values given by them are however affected by many disadvantages and variables not the least of which are methodical factors In addition, they usually are

REVIEW OF THE LITERATURE

DEFINITIONS, PRINCIPLES AND METHODS IN BLOOD AND PLASMA RHEOLOGY AND VISCOMETRY

Because of excellent recent articles concerning the rheological properties of blood, various rheological parameters and instruments, as well as disturbances of microcirculation, a detailed review in this connection is unnecessary The reader is referred to the papers of Bayliss (1960), Gelin (1961), Haynes (1961), Merrill & Wells (1961), Wells & Merrill (1961 a, b), Dintenfass (1962 a, b, c, 1963 a, 1964 b, 1965 b), Eiseman & Spencer (1962), Larcan & Genetet (1964, 1965), Murray (1964), Wayland (1965 a, b), Wells (1963, 1964) and Larcan *et al* (1965 a, b)

Concepts of rheology and viscosity

Rheology has been termed by Bingham in 1929 as »the science of deformation and flow of all matter» (Wayland 1965 a) From this extremely broad definition the mechanics of, e g, inviscid and Newtonian fluids have been excluded, so that in its usual meaning rheology refers to mechanics of non-Newtonian fluids and solid viscoelastic materials The brevity of the term has led to many applications, of which *biorheology* and *hemorheology* are examples

Viscosity can be simply defined as the property of a rheological material (fluid) to resist the flow Viscosity *in principle, however, is not a simple* and easily defined concept, where non-*Newtonian fluids such as blood and* its components are concerned (Gelin 1961, Wells & Merrill 1961 a, b, Dintenfass 1964 b, Wayland 1965 a) Expressed in rheological terms, viscosity is the ratio of *shear stress* (force imposed per unit area of fluid plane — dyn/cm²) *to shear rate* (= *velocity* gradient, i e, difference in the velocities of two fluid planes divided by the distance between them — $\frac{\text{cm sec}}{\text{cm}} = \text{sec}^{-1}$)

Flow properties of biological fluids, in general, have been reviewed in detail by Merrill & Wells (1961), Dintenfass (1964 b) and others Without exception the fluids of biological sig-

In rotating cylinder (Couette type) viscometers the flow model is much simpler in principle than in other types, and it is possible to obtain data in the form of a diagram from which the absolute viscosity can be calculated. With advanced instrumentation the cone-in-cone viscometer of Dintenfass (1962 b, 1963 a) and the G D M viscometer (Cokelet et al 1963) it has become possible to reach very low (< 1 sec ¹) rates of shear and to investigate the rheological properties of native blood near the zero flow, and thus to obtain many remarkable new data (Dintenfass 1962 a, 1963 b, 1964 d Wells 1964 1965 b, Wells & Merrill 1961 a Wells et al 1964, Merrill 1965, Merrill *et al* 1963 a, b 1964 a b 1965 b)

The principles, details, use, advantages and weak points of these new, constantly developing instruments are obtainable in, in addition to the original papers also the survey by Wayland (1965 b)

Other instruments and measurement techniques in blood viscometry — The two main categories of viscometers mentioned above form the principal equipment in the study of blood plasma and serum There exist however some instruments which in principle also can give viscosity values, but their use has been rather limited. An electronic continuously recording ultrasonic viscometer can be used for e g serum viscosity determination and in blood coagulation studies (Yesner *et al.* 1951)

Flow-out viscometry, which in a way is a combination of *in vitro* and *in vivo* measurements (a volume of blood flowing through a calibrated needle or tube introduced into a blood vessel of a living subject), has been used, after the pioneering study of Hurthle (1900) by Pirofsky (1953), Gousios & Shearn (1959), Dreizen (1962), Frasher *et al* (1965) and others

Anticoagulants and blood viscosity — Whether anticoagulants change the physicochemical properties of blood *in vitro*, above all whether they reduce the shear rate dependence of viscosity as claimed by Gousios & Shearn (1959), Copley (1960), Wells & Merrill (1961 a), Dintenfass (1962 b c) and Dreizen (1962) or do not affect the viscosity, as stated by Eckstein *et al* (1942), Galluzzi *et al* (1964), Rand *et al* (1964) and Mayer & Kiss (1965), seems as yet an unsettled methodological problem. The answer presumably is to be found in the variability of the techniques and in the amounts and qualities of anticoagulants used. In the last mentioned reports in which 5—10 units of heparin or 1 mg of EDTA per ml of blood were used no significant differences were found as compared to untreated blood samples, but with oxalate the results show some discrepancy In view of the above findings the reliable reproducibility of the results the lack of haste, and the possibility for repeated determinations with the same sample when anticoagulants are used makes their use in viscosity measurements superior to the disadvantages often encountered with untreated specimens

not applicable as such to circumstances *in vivo*

For the proper understanding of the limitations and advantages of the various methods and of the results achieved by them, a short general description of the viscometers presently used in hemorheology may be useful In the following representation the classification given by Wayland (1965 b) is followed in the main lines, for details the reader is referred to the citations of his review

The major types of viscometers nowadays applicable to hemorheological studies are the following

Capillary viscometers — Until 1961, with rare exceptions (Brundage 1934), the viscosity of blood and plasma (serum) was determined mostly with capillary instruments Usually these have been modifications, in one form or another, of Ostwald's U-tube viscometers, in which the viscosity is expressed as a function of the rate of flow through the tube The complexity of blood, which gives it its non-Newtonian flow properties, together with the known unequal flow model in capillaries (Wayland 1965 b) makes the quantitation of shear stress to shear rate in a capillary tube extremely difficult (Wells & Merrill 1961 a, Merrill 1965) Without more closely specifying the limitations of capillary viscometry, which have been discussed by Wells *et al* (1961) and Wayland (1965 b), one must admit its inability to reach rates of shear low enough to best serve to differentiate between the viscosities of normal and pathological samples of blood and plasma (Dintenfass 1963 a, b, Wells 1964)

A capillary viscometer thus is far from an ideal instrument for non-Newtonian fluids with respect to the definition of their viscosity However, knowing its limitations as an absolute instrument and as to the range of low rates of shear, one can gain useful information on the apparent viscosity with capillary apparatus using a sensitive pressure transducer in combination with other carefully controlled experimental conditions (Charm & Kurland 1962, Ayrivie 1963, Harkness 1963, Dintenfass 1964 b, Wells 1964, Mayer 1965, Merrill 1965) Rheologically, the data from measurements with fixed rates of shear apply only to these specific circumstances and do not give an exact picture of the flow properties of the sample in other situations In view of this, much of the previous data on blood rheology is specific However, the relative ease of its use, cheapness and rapidity, with good reproducibility of the results, have made tube viscometers widely used instruments, especially in clinical studies of plasma and serum

Rotational viscometers — In 1961 Wells, Denton and Merrill as well as Gelin and his co-workers reported studies on the viscosity of blood and plasma with a Brookfield cone plate viscometer With it they were able to record absolute values of shear stress and rate of shear and to show the shear rate dependence of the viscosity of biological fluids

fluidity This explains the fluidity of blood even at hematocrit values of 95—100 per cent as well as the surprisingly low relative viscosity of blood

White blood cells and platelets

In normal health the significance of leucocytes and platelets in whole blood viscosity *in vitro* has been found to be negligible (Merrill & Wells 1961, Larcan *et al* 1965 b), but increase of blood viscosity has been reported in leukemias (Stephens 1936 Dintenfass 1965 c) Some of the circulatory symptoms encountered in these diseases are also suspected to be caused by elevated viscosity

Plasma and its constituents

The rheology of plasma will be dealt with in greater detail in the following section of the review In this connection attention will be paid to some recent low shear rheologic studies on the effect of plasma proteins on the viscosity of whole blood and red cell suspensions

Normally the red cells contribute to the viscosity of blood more significantly than does the viscosity of plasma and rather remarkable changes in plasma proteins are needed before their effect becomes visible in the viscosity values of blood if studied by high shear capillary techniques

However at very low rates of shear, i e in conditions approaching flow stasis in which the viscosity of blood normally increases, even quite small alterations in some proteins may by their interaction with red cells influence the viscosity values After the classical works of Fahraeus (1921, 1929) the studies of, e g , Merrill (1965) and Wells (1965 a) and their colleagues (Merrill *et al* 1965 a, b) have recently shown that increased concentrations of fibrinogen and globulins enhance the red cell aggregation by presumably influencing the surface characteristics of erythrocytes (surface charges protein coating etc) and by creating red cell — protein networks At low flow velocities these factors, of which aggregation usually dominates lead to a marked increase in blood viscosity (the so-called structural viscosity), which increment of viscosity is according to Dintenfass reversible and exhibits thixotropic properties (Dintenfass 1964 b Wells 1964)

If a stagnant flow situation has developed, a certain minimum stress is required for this structural viscosity to yield and for flow to be produced Several studies have established the essential role of fibrinogen in bringing about the yield value of blood (Copley *et al* 1942 Dintenfass 1962 b 1964 d, Merrill *et al* 1963 a 1964 a, Wells *et al* 1964) This is comprehensible, since the yield stress in blood is caused by the aggregation of red cells (Merrill 1965), on which fibrinogen of normal plasma proteins is known to have the most pronounced effect (Fahraeus 1921 1929)

Lipids — The *effects* of various blood lipids have received relatively

The viscosity of blood is known to be affected by a variety of factors, many of which, in addition, are influenced by each other. Briefly, according to Dintenfass (1964 b), viscosity of blood is determined by four mechanisms. The *hematocrit value, the degree of aggregation of the red cells, the viscosity of the plasma, and the internal viscosity of the red cells,* of which the last three are thixotropic in nature (for the definition of thixotropy, see e.g. Dintenfass 1964 c). Only some principal determinants of blood viscosity are briefly presented below in their relation to measurements *in vitro*.

Since viscosity varies according to the circumstances of measurement the term »apparent» viscosity has been proposed to describe the value of the ratio shear stress/rate of shear in a particular condition. Thus apparent viscosity would be the right expression when data on the viscosity of blood are given, but for the sake of convenience »apparent» is usually omitted. However, the statement of data on the viscosity of fluids with non-Newtonian flow properties without specifying the experimental conditions is valueless.

Red blood cells

The non-Newtonian behavior of blood has been shown to result mainly from the presence of red cells (Bayliss 1960, Merrill & Wells 1961, Dintenfass 1962 a). Almost every property of this cell modifies the apparent viscosity of the system in which they are suspended.

The known relation of *the red cell concentration (hematocrit)* to the viscosity values of blood has been demonstrated in numerous studies (reviewed, e.g., by Wells & Merrill 1961 b, 1962, Dintenfass 1962 a, 1964 a, Erslev & Atwater 1963, and by Strumia & Phillips 1963). In capillary (high shear) studies the viscosity — hematocrit relation has been found to be nearly linear to hematocrit values up to 40—50 per cent, but with higher values the viscosity *of blood has increased exponentially*. Studies with rotational viscometers (Gelin 1961, Wells & Merrill 1961 a, b, 1962, Dintenfass 1962 a, b, 1964 a, Merrill *et al.* 1963 b, Rand *et al.* 1964, Larcan *et al.* 1965 b), have demonstrated the importance of lower rates of shear and of the temperature in this viscosity — hematocrit relation.

Although the role of hematocrit is decisive, the *size* (Strumia & Phillips 1963) and *shape* (Erslev & Atwater 1963, Dintenfass 1964 c) of the red cells have been noted to influence the apparent viscosity of whole blood. Likewise, all factors altering these properties, as for instance, *osmolality and pH* (Wells *et al.* 1963), can affect the viscosity.

Dintenfass (1962 a, 1964 a, c) has demonstrated, moreover, that the interior of the red cells has properties of a complex elastic fluid and a capacity for variation in its *internal viscosity or*

fluidity This explains the fluidity of blood even at hematocrit values of 95—100 per cent as well as the surprisingly low relative viscosity of blood

White blood cells and platelets

In normal health the significance of leucocytes and platelets in whole blood viscosity *in vitro* has been found to be negligible (Merrill & Wells 1961 Larcan *et al* 1965 b), but increase of blood viscosity has been reported in leukemias (Stephens 1936, Dintenfass 1965 c) Some of the circulatory symptoms encountered in these diseases are also suspected to be caused by elevated viscosity

Plasma and its constituents

The rheology of plasma will be dealt with in greater detail in the following section of the review In this connection attention will be paid to some recent low shear rheologic studies on the effect of plasma proteins on the viscosity of whole blood and red cell *suspensions*

Normally the red cells contribute to the viscosity of blood more significantly than does the viscosity of plasma and rather remarkable changes in *plasma proteins* are needed before their effect becomes visible in the viscosity values of blood if studied by high-shear capillary techniques

However, at very low rates of shear i e in conditions approaching flow stasis in which the viscosity of blood normally increases, even quite small alterations in some proteins may by their interaction with red cells influence the viscosity values After the classical works of Fahraeus (1921, 1929) the studies of e g, Merrill (1965) and Wells (1965 a) and their colleagues (Merrill *et al* 1965 a b) have recently shown that increased concentrations of fibrinogen and globulins enhance the red cell aggregation by presumably influencing the surface characteristics of erythrocytes (surface charges protein coating, etc) and by creating red cell — protein networks At low flow velocities these factors of which aggregation usually dominates lead to a marked increase in blood viscosity (the so-called structural viscosity), which increment of viscosity is according to Dintenfass reversible and exhibits thixotropic properties (Dintenfass 1964 b Wells 1964)

If a stagnant flow situation has developed, a certain minimum stress is required for this structural viscosity to yield and for flow to be produced Several studies have established the essential role of fibrinogen in bringing about the yield value of blood (Copley *et al* 1942, Dintenfass 1962 b 1964 d, Merrill et *al* 1963 a 1964 a, Wells *et al* 1964) This is comprehensible, since the yield stress in blood is caused by the aggregation of red cells (Merrill 1965), on which fibrinogen of normal plasma *proteins* is known to have the most pronounced effect (Fahraeus 1921, 1929)

Lipids — The effects of various blood lipids have received relatively

DETERMINANTS OF BLOOD VISCOSITY

The viscosity of blood is known to be affected by a variety of factors, many of which, in addition, are influenced by each other. Briefly, according to Dintenfass (1964 b), viscosity of blood is determined by four mechanisms. The hematocrit value, the degree of aggregation of the red cells, the viscosity of the plasma, and the internal viscosity of the red cells, of which the last three are thixotropic in nature (for the definition of thixotropy, see e.g. Dintenfass 1964 c). Only some principal determinants of blood viscosity are briefly presented below in their relation to measurements *in vitro*.

Since viscosity varies according to the circumstances of measurement the term »apparent» viscosity has been proposed to describe the value of the ratio shear stress/rate of shear in a particular condition. Thus apparent viscosity would be the right expression when data on the viscosity of blood are given, but for the sake of convenience »apparent» is usually omitted. However, the statement of data on the viscosity of fluids with non-Newtonian flow properties without specifying the experimental conditions is valueless.

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Lipids — The effects of various blood lipids have received relatively

little attention as possible determinants of blood viscosity as compared to cell and protein factors Apparently due to methodical variations the results of the few studies are somewhat contradictory, as reviewed by Charm *et al* (1963), Konttinen & Somer (1963) and Larcan *et al* (1965 b) It seems that even when the viscosity of blood is measured at low rates of shear (Charm *et al* 1963, Merrill *et al* 1964 b, Rand *et al* 1964) or by high-shear capillary methods (Swank 1956, Watson 1957, Charm *et al* 1963) the changes are too small to reveal specific influence by lipids

FACTORS DETERMINING PLASMA AND SERUM VISCOSITY

The viscosity of plasma and serum may at first seem a much less interesting subject of study than that of whole blood One of the fundamental physical characteristics of colloidal solutions, however, is their viscosity, which, especially in the case of mixed protein solutions, is not a simple property as one might assume on the basis of the simplicity of the commonly used methods for its determination

In medical literature Hess and Cobure (1950) probably have the most thoroughly defined the viscosity of protein solutions as well as the numerous variables affecting it Only a few of these determinants pertinent to the scope of the present work, i e, those connected with plasma protein characteristics, will be briefly reviewed here for the purpose of orientation It is noteworthy that most of these factors which influence the viscosity of macromolecular solutions have been known for years in the fields of industrial rheology and polymer science (Staudinger 1950, Jirgensons 1958, Yang 1961)

Properties of some plasma proteins and viscosity

Concentration — Since the resistance to flow in liquids is caused by attractive forces acting between the solute molecules, as a consequence of which heterogeneous flow gradients are produced, it is clear that the viscosity of any colloidal solution increases with an increasing concentration of the solute Most studies of the viscosity of plasma, serum or solutions of isolated blood proteins have confirmed this relationship (e g, Houston *et al* 1949, Kreuzer 1950, Eastham 1954 a, b, Jahnke *et al* 1958, Steel 1959 a, b, Lawrence 1961, Barth 1964, Larcan *et al* 1965 b) In principle it is non-linear if viscosities of sufficiently concentrated solutions are studied The shape of the concentration — *viscosity* curve, however is dependent mainly on the protein characteristics, as will be seen in the following

The various theoretical aspects connected with the *effect* of concentration as well as of other properties of pro-

teins on viscosity have been well reviewed by, e g , Bull (1951), Jahnke et al (1958) and Jirgensons (1958)

Molecular characteristics — The size of a protein molecule has of course, its own undisputable influence on the viscosity, but in regard to other characteristics it is surprisingly slight The viscosity of for instance, a spheroprotein solution (e g β_1-lipoprotein) is practically independent of the particle size (Cohn et al 1944, Oncley et al 1947 Jirgensons 1958) provided that the volume fraction is the same Conversely with linear proteins the viscosity correlates to their size (molecular weight) *if the concentrations are* unchanged and some other special requirements are fulfilled.

The most decisive factor among the determinants of the plasma viscosity is the *shape* of the protein molecules in the solution It is the difference of this molecular parameter that mainly explains the various responses of concentration — viscosity and size — viscosity relationships between the solutions of globular and linear proteins While spherocolloids (such as serum albumin) exhibit only a slight and up to a certain concentration almost linear dependence between the viscosity and the concentration (Lawrence 1950 Steel 1959 b Eastham & Morgan 1965) the viscosity of fibrous proteins can be very high even in dilute solutions, which is seen as an early clearcut non linearity of the concentration — viscosity correlation (Hess & Cobure 1950 Jahnke et al 1958 Eastham & Morgan 1965) Accordingly the viscosity of a 2 per cent fibrinogen solution has been reported to be about the same as those of 25 per cent albumin and 15 per cent globulin solutions or that of whole blood (Cohn et al 1944)

No experimental data appear to have been published of the influence of *deformability (flexibility)* of the plasma protein molecules on the viscosity values From the colloid science it is known that the flexibility of macromolecules is connected with the quality of the solvent (Jirgensons 1958 Yang 1961) In »good» solvents the intrinsic viscosities are higher than in »poor» ones, because in the former the molecules are well streched out

Hydrostatic state (solvation) — Proteins and carbohydrates are known to be strongly hydrophilic substances Hence in addition to the discussed characteristics of the protein molecules their degree of hydration (solvation), i e attachment of the solvent molecules to proteins influences the viscosity of protein solutions (Oncley 1941, Edsall 1953) Increased viscosity is thought to be caused partly by impaired flexibility partly because swollen molecules occupy a greater volume, and partly because of the occlusion of solvent molecules between and inside the protein molecules (Jirgensons 1958)

One of chief factors regulating the degree of solvation of proteins is their carbohydrate content Accordingly Hollmann and Eggers (1962) have shown a good correlation between the serum protein bound carbohydrate content and the serum reduced specific viscosity However the plotting of respective data of Baars et al (1958) in

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seven cases of macroglobulinemia showed a considerable skew

Electrical charge of the molecules, pH and ionic force of the solution — The effect of these factors on viscosity seems, too, to be due largely to changes in the shape and molecular volumes of the proteins (Jirgensons 1958), although the exact effect that these complicated variables and the degree of hydration exert on the viscosity of plasma protein solutions obviously has not been established (Bull 1951)

The influence of pH changes on the viscosity of plasma proteins has been studied by, among others, Eirich & Sinnreich (1937), Jirgensons (1958), Steel (1959 b), Joly (1962), Smith *et al* (1965) From the data of Steel (1959 b) it appears that especially in the case of proteins with non-globular shape and great size the pH of solutions can influence the viscosity values quite markedly if pH variations are great The importance of noting the effect of this variable has been pointed out also by Kreuzer (1950)

Temperature sensibility of proteins — Although the viscosity of normal sera has been found to show in the range 5—40°C a very slight increase with falling temperature, the temperature should be accurately controlled in all viscosity measurements since it can be one of the most powerful determinants of the viscosity

Normal globulins have been reported to contribute more to the temperature dependence of the viscosity of protein solutions than albumin (Sandkuhler 1958) Most clearly the influence of differences in the protein molecular properties on the thermal dependence of the viscosity will appear, however, in case of pathological proteins, as will be seen in the discussion on page 29

Lipids and other non protein components of plasma

As pointed out above in connection with blood viscosity, the effect of various *lipids* on plasma viscosity has been studied relatively little, and no conclusive remarks can be made at this stage of investigations What has been said above seems to fit also the viscosity of plasma Merrill *et al* (1964 b) studied the effect of a fatty meal on the viscosity of plasma and in one of the two test persons they found an increase in the (fibrinogen-dependent) yield shear stress of blood, this increment was especially evident at low temperatures A similar finding on the effect of lipids was made by Dintenfass (1965 a), who found that at 20°C the viscosity of lipid-containing plasma was fivefold that without lipids, but at 37°C the effect was not noted

The effects of other non-protein components of plasma have been reported to be unimportant in regard to viscosity (Lawrence 1961, Skovborg *et al* 1966), or if they slightly modify the viscosity this action possibly is mediated through changes in the proteins

Flow properties of plasma and serum

The effect of experimental conditions in the determination of plasma and serum viscosity on the values obtained

is intimately connected with the question of the possible non-Newtonian flow properties of these solutions

While the influence of the velocity gradient on the viscosity values of plasma and serum or of isolated plasma protein solutions was discussed already by e g, Oncley (1941) and Edsall (1953) and observed by Kreuzer (1950), Copley *et al* (1960) and others, it was only after the works of Wells and Merrill (1961 a b) that the question was brought under serious consideration However it has remained in the backround of rheological peculiarities of whole blood. Still, at the moment there seems to be uncertainty concerning the nature of the flow of normal plasma and serum (Dintenfass 1965 a, Merrill 1965 Groth & Thorsen 1965)

In every case there is sufficient evidence that pathological plasma with an increased viscosity can exhibit clear non Newtonian and thixotropic properties (Cerny *et al* 1962 Ayrivie 1963, Harkness 1963, Merrill *et al* 1963 a, Rand *et al* 1964, Dintenfass 1965 a) This also means that ideally the determinations of the viscosities of plasma and serum should be made with viscometers capable of easily quantitating shear stress and rate of shear, and preferably also to operate at very low flow gradients

As factors that cause the stated non-Newtonian properties have been proposed the molecular orientation of asymmetric pathological proteins in the direction of shear, phenomena connected with hydration and solvent occlusion between molecules, the mutual interactions between molecules due to, for instance, ionization and possible molecular aggregations into protein networks by weak bonds (Jirgensons 1958 Merrill & Wells 1961) However with rising temperature these anomalous flow properties of solutions containing asymmetric proteins approach, or become, Newtonian because of the counteracting effect of thermal motion on molecular orientation, *among other* reasons (Jirgensons 1958)

VISCOSITY STUDIES IN DYS- AND PARAPROTEINEMIAS

Classification of dys and paraproteinemias

Somewhat different nomenclature for serum proteins as well as for states showing deflections from their normal pattern is in use today Especially the terminology concerning the immunoglobulins — γ-globulins having antibody function — has been confusing until quite recently but since the proposal of a WHO Meeting on the Nomenclature in 1964 the three principal human immunoglobulins have been termed γG-, γA- and γM-globulins This terminology as well as the following ones will also be used in this report

Dysproteinemia has been defined by Wuhrmann (Wuhrmann & Marki

1963) as a state where one or several of the plasma protein fractions have been quantitatively altered due to disturbance in protein synthesis usually caused by a disease. In this meaning the term is used in the present study. In a wider sense used by many workers the term dysproteinemia covers all pathological deflections from the normal plasma protein pattern (e.g. Riva 1960), thus also including the paraproteinemias and cryoproteinemias (Streiff 1959).

The term *paraproteinemia* is currently used clinically to define a case in which the serum contains functionally inert, electrophoretically homogeneous abnormal protein(s) belonging to the immunoglobulin group, but lacking some antigenic determinants of the corresponding normal immunoglobulin. This type of globulins are also designated as »M-components», »M- or abnormal serum globulins» (Heremans *et al.* 1961). Paraproteinemias have been most often found in association with neoplastic diseases of the lymphoplasmoreticular system, i.e. in cases of multiple myeloma (γG-, γA- and Bence Jones-like micromolecular γμ-paraproteinemias), Waldenström's macroglobulinemia (γM-paraproteinemia) and related conditions, but also in other malignancies and in apparently healthy aged persons (Heremans *et al.* 1961).

Cryoglobulinemia is a term for a group of rare serum globulins having the common, unique property of precipitating, gelling or crystallizing in cold (Ritzmann & Levin 1961, Werth 1964). In most instances these cryoproteins occur in cases of multiple myeloma, but have also been noted in a variety of other diseases (Ritzmann & Levin 1961).

Plasma and serum viscosity as a clinical laboratory test

Despite its obvious usability as a clinical test the determination of plasma or serum viscosity has not gained acceptance comparable to other non-specific laboratory tests used to indicate alterations in the blood proteins (Harkness 1963). However, since 1940 several comparative studies of the erythrocyte sedimentation rate and plasma viscosity, recently reviewed by Lawrence (1961), Harkness (1963) and Eastham & Morgan (1965), have confirmed the better sensitivity and the numerous advantages of the latter both in technical respects and in clinical assessment of the activity of the disease by plasma protein changes. The reasons for this state of clinical viscosity tests have been discussed by, among others, Jahnke *et al.* (1958), Harkness (1963) and Dintenfass (1965 a). The lack of standardized generally accepted methods and experimental conditions, also fulfilling the rheological demands set by the non-Newtonian nature of pathological plasma, has been considered to be the principal cause, already because of the difficulties of correlating normal values and the results achieved. Therefore, the present author does not consider it necessary to give here the only slightly diverging normal ranges of plasma and serum viscosity values

found by various workers which are readily obtainable from the papers of e g, Jahnke et al (1958), Riva (1960), Lawrence (1961), Steel (1963) Fahey et al (1965) and Eastham & Morgan (1965) The normal values for the viscosity of serum relative to water seem to range between 1 4 and 1 95 and the respective values for plasma have been reported to be about 20 per cent higher

As has been pointed out the determination of plasma viscosity has been used to some extent as a clinical laboratory test in several (mostly infectious) diseases to indicate the dysproteinemic plasma protein changes that are characteristic of these states (e g, Houston et al 1949 Lawrence 1950 1961 Eastham 1954 a b Harkness 1963 Eastham & Morgan 1965) Most of these workers have concluded that plasma viscosity is a more reliable indicator of the dysproteinemic plasma protein pattern particularly of the changes in the fibrinogen and globulin fractions than the erythrocyte sedimentation rate and that it can well be used in the assessment of the clinical activity of the disease

Viscosity studies in macroglobulinemia Waldenstrom (MW) and multiple myeloma (MM)

The study of serum and plasma viscosities has gained for comprehensible reasons its greatest use and advantage in the characterization especially of the paraproteinemias.

Perhaps the principal credit for this in paraproteinemias has to be attributed to Waldenstrom, who already in his famous article on macroglobulinemia (1944) seemed to be fully aware of the possibilities which the relatively simple viscometric technique can give to clinical differentiation of the disease described by him from other hyperglobulinemias

After the first two cases of primary macroglobulinemia reported by Waldenstrom nearly 400 cases have so far been published in various connections The perusal of the literature revealed that in more than 50 papers dealing with MW and including more than 200 cases, the serum viscosity (rarely the plasma or whole blood viscosity) has been stated as one of the parameters in the case reports and clinical series Most chapters of medical textbooks (e g Gellhorn 1963), handbooks on serum proteins (Riva 1960 Wuhrmann & Marki 1963) and monographs (e g Streiff 1959) presenting the disease mention the elevated serum viscosity as one of its diagnostic and pathogenetic features However despite the many excellent original reports concerning serum viscosity studies with extensive bibliographies there is to the author s knowledge no fairly complete review of serum viscosity and its manifold clinical possibilities in MW and MM

Therefore it seemed worth while to review the former viscosity studies in these diseases. Already for practical reasons the papers to be referred to have been divided into various groups according to the main purpose of each

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Therefore it seemed worth while to review the former viscosity studies in these diseases. Already for practical reasons the papers to be referred to have been divided into various groups according to the main purpose of each

1963) as a state where one or several of the plasma protein fractions have been quantitatively altered due to disturbance in protein synthesis usually caused by a disease In this meaning the term is used in the present study In a wider sense used by many workers the term dysproteinemia covers all pathological deflections from the normal plasma protein pattern (e g Riva 1960), thus also including the paraproteinemias and cryoproteinemias (Streiff 1959)

The term *paraproteinemia* is currently used clinically to define a case in which the serum contains functionally inert, electrophoretically homogeneous abnormal protein(s) belonging to the immunoglobulin group, but lacking some antigenic determinants of the corresponding normal immunoglobulin This type of globulins are also designated as »M-components», »M- or abnormal serum globulins» (Heremans *et al* 1961) Paraproteinemias have been most often found in association with neoplastic diseases of the lymphoplasmoreticular system, i e in cases of multiple myeloma (γG-, γA- and Bence Jones-like micromolecular $\gamma\mu$-paraproteinemias), Waldenstrom's macroglobulinemia (γM-paraproteinemia) and related conditions, but also in other malignancies and in apparently healthy aged persons (Heremans *et al* 1961)

Cryoglobulinemia is a term for a group of rare serum globulins having the common, unique property of precipitating, gelling or crystallizing in cold (Ritzmann & Levin 1961, Werth 1964) In most instances these cryoproteins occur in cases of multiple myeloma, but have also been noted in a variety of other diseases (Ritzmann & Levin 1961)

Plasma and serum viscosity as a clinical laboratory test

Despite its obvious usability as a clinical test the determination of plasma or serum viscosity has not gained acceptance comparable to other non-specific laboratory tests used to indicate alterations in the blood proteins (Harkness 1963) However, since 1940 several comparative studies of the erythrocyte sedimentation rate and plasma viscosity, recently reviewed by Lawrence (1961), Harkness (1963) and Eastham & Morgan (1965), have confirmed the better sensitivity and the numerous advantages of the latter both in technical respects and in clinical assessment of the activity of the disease by plasma protein changes The reasons for this state of clinical viscosity tests have been discussed by, among others, Jahnke *et al* (1958), Harkness (1963) and Dintenfass (1965 a) The lack of standardized generally accepted methods and experimental conditions, also fulfilling the rheological demands set by the non-Newtonian nature of pathological plasma, has been considered to be the principal cause, already because of the difficulties of correlating normal values and the results achieved Therefore, the present author does not consider it necessary to give here the only slightly diverging normal ranges of plasma and serum viscosity values

Table 1 VISCOSITY IN CASE REPORTS OF MACROGLOBULINEMIA WALDENSTRÖM

Authors	Year	Number of cases	Serum relative viscosity	Method	Temperature	Total protein conc.	Remarks
Dalgaard	19.0	1	3 8	Ostwald	37 C	7 4	Cryoglob +
Tischendorf & Hartmann	1950	1	gelification at room temp			13 5	Sample gelified in the *viscometer*
Gard et al	1952	1	5 7	n r	n r	12 0	Electron microscopy of M glob molec
McFarlane et al	1952	1	Blood viscosity was anomalous	n r	n r	8 7	M w of paraprot and axial ratio determ.
Schaub	1952	3	2 4 3 4 3 1	n r	n r	I 8 1 II 8 5 III 10 0	II Cryoglob +
Braunsteiner et al Petermann & Braunsteiner	1954	1	2.2	Ostwald	37 C	8 6	Cryoglob +
Hule & Wiedermann	1954	1	3 7	n r	n.r	10 8	$S_{20\,w}$ = 15 9 = 44 3 %
diGuglielmo & Antonini	1955	1	TVI 120	n r	n r	n r	
Long et al	1955	1	Blood η_{rel} = 1 65	Ostwald	22 —24 C	7 3	Coagulation studies
Burkmann et al	19.6	3	I & II erhöhte Werte III normal	n r	n r	I 9 0 II 11 0 III 6 2	
Hans et al	19.6	2	2 7 1 6	Hess	n r	I 8 9 II 8 1	M fr = 13 7 % M fr = 13 4 %
Regniers et al	1956	1	η_{sp} = 20	Ostwald	n r	13 0	M-frs = 66 0 %
Bousser & Boivin	1957	1	plasma η_{rel} = 21 6	n r	25 — 4 C	10 9	
Bregnballe	1957	1	4 9	n r	13 37 C	10 9	M_1 fr = 20 0 % M -fr = 6 0 %
Jannes et al	1961	2	4 5 2 1	own capill	24 C	I 11 3 II 8 7	I M frs = 60 4 % II M frs = 42 4 %
Kok	1961	1	11 4	n r	25 C	9 6	
Podivinsky et al	1962	1	in fig form	Ostwald	37 — 4 C	8 6	Cryogelglob = 2 6 g%
Ritzmann & Levin	1962	2*	2 0 2 0	Ostwald	37 — 0 C	I 7 5 II 7 0	*Cold-agglutinin dis
Robinson	1962	1	plasma η = 15 cp	n r	20 C		
Kok et al	1963	3	9 0 2 4 3 4	n r	25 C	I 11 5 II 8 7 III 8 0	M-frs = 58 5 % M-frs = 14 0 % M frs = 27 0 %
Campbell & Boenisch	1964	1	2 1	Ostwald	37 C	6 3	
Mancini et al	1964	1	in fig against temperature	n r	33 —58 C	10 7	*Cryomacroglob* = 40 %
Streiff (according to Genetet)	1964	4	plasma ad 8 cp	Lecomte de Nouy	n r	n r	
Nutter & Kramer	1965	1	9 1	Cannon Fenske	37 C	8 6	Macrocryogelglob

n r = not reported

report It is hoped that this grouping will at the same time serve to give a picture of the several aspects and clinical usefulness of plasma and serum viscosity measurements in cases with paraproteinemia

Case reports including viscosity data

Because of the stimulating effect of Waldenstrom's well studied cases, serum viscosity studies have been included in numerous subsequent case reports of MW and also of MM Reports of cases of MW, in which serum viscosity has been recorded as a secondary parameter, are summarized, with some pertinent data, in table 1 Papers with viscosity studies in MM are considerably fewer Since a large proportion of the cases of MM with serum viscosity data are comparable to the cases of MW shown in table 1, all the reports of MM with viscosity studies are collected in table 2 These tables are presented principally in order to give a picture of the wide range of serum viscosities as well as to show the rather heterogeneous experimental conditions and methods used Moreover, the referred papers contain several well studied cases that are noteworthy also in other respects than viscosity

Clinical symptoms due to hyperviscosity and their treatment

Because of their relatively easy observability, *ocular manifestations* in patients with MW have been noted in several cases with correlative viscosity findings Since the description of »*fundus paraproteinaemicus*» by Berneaud-Kotz & Jahnke (1954) cases with *retinal* changes at least partly due to serum hyperviscosity have been described among others by Danis *et al* (1955), Korsten & Berneaud-Kotz (1956), Ackerman (1962), Carr & Henkind (1963), Fink *et al* (1964) and Ashton (1965) In addition to the above referred reports, some of which included observations on MM, cases of MM with *microcirculatory disturbances* in the eyes have been published by Marmont *et al* (1957), who compared *conjunctival* sludging, red cell aggregation *in vitro* and coincident plasma viscosity values, with consistent findings

The varied manifestations of this »*serum hyperviscosity syndrome*» have been recently summarized by Fahey (1963) and Fahey *et al* (1965) with pertinent discussion of the pathogenesis of the symptoms in the syndrome

The hyperviscosity syndrome, al though reported in connection with MM (e g Andre *et al* 1952, Brauman *et al* 1953, Carr & Henkind 1963 Viala *et al* 1963, Smith *et al* 1965) seems to be considerably more rare in this disease than in MW Smith *et al* (1965) reported two well studied cases of MM exhibiting high serum viscosities due to *in vivo* aggregation of , G-globulin In both cases vigorous plasmapheresis was required to control the dangerous symptoms

In connection with some therapeutic trials with various *drugs* or *plasma-*

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McFarlane et al	1952	1	Blood viscosity was anomalous	n r	n r	8 7	M w of paraprot and axial ratio determ.
Schaub	1952	3	24 34 31	n r	n r	I 81 II 85 III 100	II Cryoglob +
Braunsteiner et al Petermann & Braunsteiner	1954	1	2 2	Ostwald	37 C	8 6	Cryoglob +
Hule & Wiedermann	1954	1	3 7	n r	n r	10 8	$S_{20\,w}$ = 15 9 = 44 3 %
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Long et al	1955	1	Blood η_{rel} = 1 65	Ostwald	22 —24 C	7 3	Coagulation studies
Bürkmann et al	1956	3	I & II erhöhte Werte III normal	n r	n r	I 90 II 110 III 62	
Haas et al	1956	2	27 16	Hess	n r	I 89 II 81	M-fr = 13 7 % M-fr = 13 4 %
Regniers et al	1956	1	η_{sp} = 20	Ostwald	n r	13 0	M frs = 66 0 %
Bousser & Boivin	1957	1	plasma η_{rel} = 21 6	n r	25 — 4 C	10 9	
Bregnballe	1957	1	4 9	n r	13 37 C	10 9	M_1-fr = 20 0 % M_2-fr = 6 0 %
Jannes et al	1961	2	4 5 2 1	own capill	24 C	I 11 3 II 8 7	I M frs = 60 4 % II M frs = 42 4 %
Kok	1961	1	11 4	n r	25 C	9 6	
Podivinsky et al	1962	1	in fig form	Ostwald	37 — 4 C	8 8	Cryogelglob = 2 6 g%
Ritzmann & Levin	1962	2*	2 0 2 0	Ostwald	37 — 0 C	I 7 5 II 7 0	*Cold agglutinin dis
Robinson	1962	1	plasma η = 15 cp	n r	20 C		
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Campbell & Boenisch	1964	1	2 1	Ostwald	37 C	6 3	
Mancini et al	1964	1	*in fig against temperature*	n r	33 —58 C	10 7	Cryomacroglob = 40 %
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In connection with some therapeutic trials with various *drugs* or *plasma-*

Table 1 VISCOSITY IN CASE REPORTS OF MACROGLOBULINEMIA WALDENSTRÖM

Authors	Year	Number of cases	Serum relative viscosity	Method	Temperature	Total protein conc	Remarks
Dalgaard	1950	1	38	Ostwald	37 C	74	Cryoglob +
Tischendorf & Hartmann	1950	1	gelification at room temp			135	Sample gelified in the viscometer
Gard et al	1952	1	57	n.r	n r	120	Electron microscopy of *M-glob* molec
McFarlane et al	1952	1	Blood viscosity was anomalous	n r	n r	87	M w of paraprot and axial ratio determ
Schaub	1952	3	24 34 31	n.r	n r	I 81 II 85 III 100	II Cryoglob +
Braunsteiner et al Petermann & Braunsteiner	1954	1	22	Ostwald	37 C	86	Cryoglob +
Hule & Wiedermann	1954	1	37	n r	n r	108	$S_{20w} = 159 = 443\%$
diGuglielmo & Antonini	1955	1	TVI 120	n r	n r	n r	
Long et al	1955	1	Blood $\eta_{rel} = 165$	Ostwald	22 —24 C	73	Coagulation studies
Bürkmann et al.	1956	3	I & II erhohte Werte III normal	n r	n r	I 90 II 110 III 62	
Haas et al	1958	2	27 18	Hess	n r	I 89 II 81	M fr = 137 % M fr = 134 %
Regniers et al	1958	1	$\eta_{sp} = 20$	Ostwald	n r	130	M-frs = 660 %
Bousser & Boivin	1957	1	plasma $\eta_{rel} = 216$	n r	25 — 4 C	109	M_1-fr = 200 %
Bregnballe	1957	1	49	n r	13 37 C	109	M fr = 60 %
Jannes et al	1961	2	45 21	own capill	24 C	I 113 II 87	I M frs = 604 % II M frs = 424 %
Kok	1961	1	114	n r	25 C	96	
Podivinsky et al	1962	1	in fig form	Ostwald	37 — 4 C	86	Cryogelglob = 26 g%
Ritzmann & Levin	1962	2*	20 20	Ostwald	37 — 0 C	I 75 II 70	*Cold-agglutinin dis
Robinson	1962	1	plasma η = 15 cp	n r	20 C		
Kok et al	1963	3	90 24 34	n r	25 C	I 115 II 87 III 80	M frs = 58.5 % M frs = 140 % M-frs = 270 %
Campbell & Boenisch	1964	1	21	Ostwald	37 C	63	
Mancini et al	1964	1	in fig against temperature	n r	33 —58 C	107	Cryomacroglob = 40 %
Streiff (according to Genetet)	1964	4	plasma ad 8 cp	Lecomte de Nouy	n r	n r	
Nutter & Kramer	1965	1	91	Cannon-Fenske	37 C	86	*Macrocryogelglob*

n r = not reported

Table 2 EARLIER VISCOSITY

Authors	Year	Number of cases	Relative viscosity of serum	plasma	blood
Bannick & Greene	1929	1	2 9—3 0		
Reimann	1932	1		7 0	
Magnus—Levy	1933 (1938)	1	37 5 = 7 4 20 = 26		
Veil (cit by M—L)	1933	1	4 18		
Burkel	1935	1	3 5		
v Keiser	1936	1	gelification	20 = 29 7 37 5 = 8 4	20 = 25 37 = 12
Albers	1937	1 (3)	37 = 3 2	20 = 4.2	20 = 7.2
Vignati & Rauchenberg	1937	1	4 4		
Stewart & Weber	1938	2	I 4.3 II 1 6		I 8 0 II 4 4
Waldenstrom	1944	3	I 2 7 II 3 2 III 6 7 (17)		
Michaud	1946	1	2 65		4 7
Hansen & Faber	1947	1	∼4 5		
Hill et al	1949	1		∼5	
Uehlinger	1949	3	I 6 4 II 2 7	III ∼7	
Lawrence	1950	1		5 7	
Andre et *al*	1952	3	I 4 = 8 4 32 = 7 8 II 15 = 200 37 = 64 III (t?) 8 5		
Waldenstrom	1952	1	3 1		
Brauman et al	1953	1		44 = 12 32 = 56	
Petersen	1953	7 (?)	no figures available		
Eastham	1954 (b)	3		I 3 6 II 4 8 III 6 0	
Brauman et al	1956	1	2 4		
Marmont et al	1957	6		plasma flow times 427 —720	
Sandkuhler & Roemheld	1957	3	I—II normal *III erhoht*		
Jahnke et al	1958	4	range 1 57—2 58 mean 2 05		
Riva	1960	15	range 1 85—8 4 mean 3.2		

Method	Temperature	Total protein conc g/100 ml	Remarks
n.r	n r	10 0	
Hess	n r	10 1	Normal plasma viscosity 1 7
Hess & Ostwald	20 —39.5 C	13 0	Reported also as case 1 by Albers
Ostwald	n.r		
n.r	n.r	13 7	
Hess	20 —37.5 C	pl 12 4 se 8 6	Reported also as case 2 by Albers
Hess	20 —37 C	11.3	
Hess	n.r	16 7	
n.r	n r	I 12.3 II 5 3	I ESR 82 Urine B J+ II ESR 17 Urine B J+
modified Ostwald	9 —37 C		TVI in all < 120
n.r	n r	10.8	B J + WBC 15 400 Leucemie plasmocellul
Ostwald	25 —43 C	8 2	Raynaud s phen.+retinopathy thromb v.retin., cryogel formation
Ostwald	32 —43 C	n.r	Cryogel-formation
modified Ostwald?	n.r	I 13 0 II 9.5 III 10.2	I TVI 133 6
Ostwald	25 C	n r	
Hess	4 —37 C	I 10.2 II 13 6 III 13 9	All cases had retinopathy epistaxis and other manifestations of hemorrhagic diathesis
Ostwald	37 C	n.r	Cryoglobulins present, results presented in a figure
Ostwald	32 —44 C	11 9	Signs from periph circ gelification at 30
Ostwald	37 C	n r	Viscosimetric determ. of fibrinogen
Ostwald	25 C	n.r	Comparison with ESR
Ostwald	n.r	8 6	Cryoglobulins and crystallizes spontaneously
O twald	25 C	n.r	Pl viscosity at 25 alwals < 200'
own	n.r	III 9 4	
Ostwald	5 —45 C	range 6.5—12.5	TVI in a case with tot.prot of 12.5 = 137 in others < 120
Hess	room temp	range 8.3—15 1	One B J paraproteinemia with tot.prot. of 9 7 g/100 ml = 1.65 (serum η_r 1)

Table 2 EARLIER VISCOSITY

Authors	Year	Number of cases	Relative viscosity of serum	plasma	blood
Bannick & Greene	1929	1	2 9—3 0		
Reimann	1932	1		7 0	
Magnus—Levy	1933 (1938)	1	37 5 = 7 4 20 = 26		
Veil (cit by M—L)	1933	1	4 18		
Burkel	1935	1	3 5		
v Keiser	1936	1	gelification	20° = 29 7 37 5 = 8 4	20 = 25 37° = 12
Albers	1937	1 (3)	37 = 3 2	20 = 4 2	20 = 7.2
Vignati & Rauchenberg	1937	1	4 4		
Stewart & Weber	1938	2	I 4.3 II 1 6		I 8 0 II 4 4
Waldenstrom	1944	3	I 2 7 II 3 2 III 6 7 (17)		
Michaud	*1946*	1	2 65		4 7
Hansen & Faber	1947	1	∼4 5		
Hill et al	1949	1		∼5	
Uehlinger	1949	3	I 6 4 II 2 7	III ∼7	
Lawrence	1950	1		5 7	
Andre et al	1952	3	I 4 = 8 4 32 = 7 8 II 15 = 200 37 = 64 III (t?) 8 5		
Waldenstrom	1952	1	3 1		
Brauman et al	1953	1		44 = 12 32 = 56	
Petersen	1953	7 (?)	*no figures available*		
Eastham	1954 (b)	3		I 3 6 II 4 8 III 6 0	
Brauman et al	1956	1	2 4		
Marmont et al	1957	6		plasma flow times 427 —720	
Sandkuhler & Roemheld	1957	3	I—II normal III erhoht		
Jahnke et al	1958	4	range 1 57—2 58 mean 2 05		
Riva	1960	15	range 1 85—8 4 mean 3.2		

STUDIES IN MULTIPLE MYELOMA (continued)

Method	Temperature	Total protein conc g/100 ml	Remarks
Ostwald	3 —37 C	I 14 4 II 5 7 III 10 0	All had cryoglobulins and TVI was in I and III 200 and 140
Ostwald	37 C	I 14.5 II 8 0	Retinopathy + v-ty of controls 1 minute
Ostwald	37 C	n.r	Compared with MW mean 10 1
Hardwicke & Squire	25 C	mean 12.9	Comparison with macroglobulinemias
Ostwald	37.5 C	n.r	Comparison with macroglobulinemias
n.r	n r	8 6	α myeloma
own, capillary	12 —37 C	13 0	Cryoglobulins present
Ostwald	37 C	9.9	
Lecomte de Nouy	n.r	n.r	
Ostwald	17 —37 C	n.r	TVI (17 /37) < 120 Dissoc with cysteamin
n.r	n.r	16 7	Typical retinopathy +
Ostwald	37 C	I 11.0 II 12.2	Hyperviscosity syndrome was relieved by plasmapheresis
Ostwald	17 —37 C		Dissociation with cysteamin reduced ηsp/c in a case γA-myeloma
Ostwald	37 C	12.0	Two paraprotein peaks

creased red cell life span. They postulated that increased serum viscosity may be one of the factors operating in the pathogenesis of anemia commonly found in MW

Comparisons of serum viscosity to clinical methods of serum protein examination

After the pioneer studies of Waldenstrom (1944 1949 1952) on the position and usability of viscosity as a clinical method, some larger comparative series of MW patients in which serum viscosity was used as an important or chief parameter have been published The serum relative viscosity levels of a series of seven cases by Baars *et al* (1958) were rather moderate (range 2 0—3 3) as compared to the ranges from later observations by Jahnke *et al* (1958) in nine typical MW cases with a range of 1 7—33 6 by Kappeler *et al* (1958) in 14 patients with a range of 2 0—16 0, Ratcliff *et al* (1963) also in 14

Table 2 EARLIER VISCOSITY

Authors	Year	Number of cases	Relative viscosity of serum	plasma	blood
Podivinsky et al	1962	3	I 4 1 II 1 3 (37°) III 2 1		
Carr & Henkind	*1963*	*2*	I 15 45 II 6 45		
Fahey	*1963*	*10*	range 2 0—4.5 mean 2 9		
Ratcliff et al	*1963*	*4*	mean 4 5		
Steel	*1963*	*several but n.r*	data in a figure		
Tidstrøm	*1963*	*1*	*increased*		
Viala et al	1963	1	*flow time 200*	data in a figure	
Campbell & Boenisch	1964	1	2 7		
Streiff (according to Genetet)	1964	1		9 2	
Tischendorf et al	1964	7	data in a figure		
Ashton	1965	1		vty of blood and plasma extremely high	
Smith et al	*1965*	*2*	I 5 8 II 24 8		
Tischendorf et al	*1965*	*21 ?(1)*	data from 1 case only as sp/c		
Vaerman et al	1965	1	5 6		

n r = *not reported, TVI = temparture* — viscosity index

pheresis in *MW* and MM, serial serum viscosity measurements have been used to indicate the effect of therapy For *instance, diGuglielmo (1960)* found that the temperature — viscosity index was reduced after prednisone treatment of two MW patients Riva (1960) and Klemm *et al* (1963) reported similar findings in their patients after therapy with cytostatic drugs

Schwab & Fahey (1960) and Schwab *et al* (1960) were the first to note dramatic reductions of increased serum viscosity by plasmapheresis with concomitant reversals of retinopathy and cardiac failure in two MW patients *In a series of* ten MW patients the mean serum relative viscosity of 12 0 could be lowered to a mean value of 3 3 after intensive serial plasmapheresis (Solomon & Fahey 1963) *Using the same series of patients* in an erythrokinetic study, Cline *et al* (1963) observed that in two of the patients the reduction serum viscosity and macroglobulin level by plasmapheresis was *associated* with an in-

STUDIES IN MULTIPLE MYELOMA (continued)

Method	Temperature	Total protein conc g/100 ml	Remarks
Ostwald	3 —37 C	I 14 4 II 5 7 III 10 0	All had cryoglobulins and TVI was in I and III 200 and 140
Ostwald	37 C	I 14.5 II 8 0	Retinopathy + v ty of controls 1 minute
Ostwald	37 C	n.r	Compared with MW mean 10 1
Hardwicke & Squire	25 C	mean 12.9	Comparison with macroglobulinemias
Ostwald	37.5 C	n.r	Comparison with macroglobulinemias
n.r	n.r	8 6	α_2-myeloma
own, capillary	12 —37 C	13 0	Cryoglobulins present
Ostwald	37 C	9 9	
Lecomte de Nouy	n.r	n.r	
Ostwald	17 —37 C	n.r	TVI (17 /37) < 120 Dissoc with cysteamin
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Comparisons of serum viscosity to clinical methods of serum protein examination

After the pioneer studies of Waldenstrom (1944 1949 1952) on the position and usability of viscosity as a clinical method some larger comparative series of MW patients in which serum viscosity was used as an important or chief parameter have been published. The serum relative viscosity levels of a series of seven cases by Baars *et al* (1958) were rather moderate (range 2 0—3 3) as compared to the ranges from later observations by Jahnke *et al* (1958) in nine typical MW cases with a range of 1.7—33 6 by Kappeler *et al* (1958) in 14 patients with a range of 2 0—16 0 Ratcliff *et al* (1963) also in 14

patients with values ranging between 1 8 and 12 5, and Steel (1963) in 11 cases with a range of 2 4—15 8 In most cases in these reports the serum relative viscosity values seem to correlate rather well to the amounts of pathological proteins in sera examined by various techniques, as for instance paper electrophoresis, ultracentrifugation and the gel diffusion precipitin technique At the same time some cases in all of these series demonstrate that the nature, state and possible special characteristics of the paraproteins can be almost equally important for the serum viscosity as their concentration is, judging from the wide deviations in the ranges of serum viscosity in sera with similar paraprotein and total protein concentrations

In seeking the reasons for the disproportionately high serum viscosity values which have grossly departed from those to be expected on the basis of the protein concentration, some reports have concluded as the most plausible explanation the possibility of *aggregation* between paraprotein molecules In two cases of macroglobulinemia this kind of aggregation was suspected to have led to a viscosity-increasing protein network (Gard *et al* 1952, Regniers *et al* 1956) Recently, in two cases of γG-myeloma (Smith *et al* 1965) and in one case of γA-myeloma (Vaerman *et al* 1965), refined immunological and ultracentrifugal serum protein analyses confirmed that polymerization of the paraproteins resulted in huge protein aggregates which evidently caused the reported high serum viscosities (see Tables 1 and 2)

This evidence agrees well with the discussed observations on the correlation of whole blood viscosity and red cell aggregation as well as with experiences on protein denaturation during which an augmentation of the *viscosity of protein solutions* has been noted (Joly 1965) It has been suggested that the mentioned viscosity increment of the latter is caused partly by the enhanced aggregation tendency of denatured proteins

Differentiation of paraproteinemias and various hyperglobulinemias by viscometry

Although macroglobulinemia is the most common cause of significantly elevated serum viscosity, a high serum viscosity in itself is not diagnostic for this state, as will be later shown and as can be observed from the viscosity values in cases of MM (Table 2, see, e g, cases reported by Andre *et al* 1952, Brauman *et al* 1953, Viala *et al* 1963, Smith *et al* 1965) However, serum viscometry has proven to be a useful additional method for the differentiation of paraproteinemias from each other and from other hypergammaglobulinemias for instance those connected to rheumatic diseases (Shearn *et al* 1963, Barth 1964) The diagnostic usefulness of viscometry can be augmented if some special characteristics of macroglobulins are taken into consideration

Perhaps the most widely used one of these diagnostic approaches is based on the greater temperature sensitivity of macroglobulins The use of Waldenstrom's temperature — viscosity index or of related indexes serves as an example of this (Jahnke *et al* 1958)

As has been pointed out, especially samples containing pathological proteins can exhibit a striking temperature sensitivity which is also reflected as an increment in their viscosity at low temperatures (Jahnke *et al* 1958, Sandkuhler 1958) Temperature-induced changes, or better, the thermal sensitivity of plasma and serum viscosity in cases of macroglobulinemia and or multiple myeloma have been studied especially by Waldenstrom (1944 1949 1952) Jahnke *et al* (1958) Ritzmann *et al* (1960 b) Dintenfass (1965 a) Tischendorf *et al* (1965) and Smith *et al* (1965) Of the pathological proteins occurring in the diseases mentioned the cryoglobulins stand out as a group of their own in view of the marked temperature dependence of their viscosity (Waldenstrom 1944 1952 Volpe *et al* 1956 Jahnke *et al* 1958 Ritzmann & Levin 1961, Podivinsky *et al* 1962)

Waldenstrom (1944) in his well-known study of macroglobulinemia observed that sera from patients with this newly recognized disease usually had a significantly higher viscosity at 13 C than at 37°C especially in comparison to the behavior of the viscosity of sera from other hyperglobulinemias notably from myeloma He proposed therefore the use of a temperature — viscosity index (TVI), which he calculated according to formula $\frac{\eta_{rel} \text{ at } 13°C}{\eta_{rel} \text{ at } 37°C} \times 100$ He noted that a TVI value over 120 often was found in sera containing abnormal γM-globulins Waldenstrom's later findings (1952), however, indicated that a TVI value over 120 can occur in some cases of hyperglobulinemia when the amount of γ-globulin exceeds 10 g/100 ml The idea of Waldenstrom's TVI but with slightly diverging lower temperatures (Jahnke *et al* 1958, Tischendorf *et al* 1964 1965) has subsequently been used widely in the viscometric differentiation of macroglobulinemia sera from other sera with elevated relative viscosity values (see Tables 1 and 2)

The causes of the enhanced thermal sensitivity of the viscosity of solutions containing pathological — either in amount or in quality — proteins have been discussed by e g Waldenstrom (1944 1952) Jahnke *et al* (1958), Ritzmann *et al* (1960 b) and recently by Dintenfass (1965 a) The proposal by Jahnke and co-authors of protein aggregation in cold as a possible reason for the phenomenon is supported by their finding that the temperature dependence of viscosity in macroglobulinemias was chiefly determined by the viscosity of the serum itself Similar findings by Smith *et al* (1965) in a case (No 2) of myeloma with *in vivo* aggregation of γG paraprotein also support this view According to Dintenfass (1965 a) the temperature-motivated changes in viscosity may be explained by corresponding

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are very few This despite that many clinical reports discussing the *in vivo* microcirculatory findings in MW and MM have stressed the significance of plasma proteins in the impaired capillary flow and in the ensuing clinical complications of these diseases (reviewed e g by Harders 1957, Wells *et al* 1962, Wells 1964, 1965 a, Dintenfass 1965 a)

It seems that only in one reported case of MW the rheological approach to plasma flow properties by rotational viscometer showed that pathological blood plasma can be strikingly non-Newtonian and show thixotropic properties (Dintenfass 1965 a) Additionally, Wells (1964) in a review announces findings of a similar trend

alterations in the *solubility of the* plasma proteins

Another means for viscometric differentiation between MW and e g MM is offered by the *dissociability of macroglobulins*, but not myeloma proteins In several *in vitro* and in few *in vivo* trials attempts have been made to lower the increased viscosity of macroglobulinemic sera with chemicals capable of depolymerizing macroglobulins to smaller 7 S components *Such trials have been carried out with cysteine* (Ishiker 1958, Ritzmann *et al* 1960 a, Tischendorf *et al* 1965), *mercaptoethanol* (Steel 1959 b, Szabolcs *et al* 1965) and *penicillamine* (Ritzmann *et al* 1960 a, b) The high serum viscosity in MM or in other hyperglobulinemias is not lowered markedly or at all by this *in vitro* procedure, whereas the viscosity of macroglobulinemic sera usually is reduced so significantly that this property can be used in the distinction of these states

Steel (1963) has introduced a method based on a fixed *protein concentration* and calls it »interpolated 7 % viscosity» *He noticed that by diluting the* serum with elevated viscosity to a protein content of 7 g/100 ml, the relative *viscosity of myeloma sera is reduced* to the normal range (below 2 0), but *in cases of* macroglobulinemia the »7 % viscosity» remains above this limit A rather similar method has been presented by Ratcliff *et al* (1963) It is founded on the different behavior of sera containing ,M« and myeloma proteins in concentrations above 5 g 100 ml protein as determined by paper electrophoresis, when submitted to calculation according *to the formula*

$$\frac{\text{serum relative viscosity}}{, + \text{M-concentration, } g/100\ ml}$$

Viscosity studies on isolated paraproteins

In some instances when macroglobulins or myeloma proteins have been isolated their viscosities have also been determined in connection with other physicochemical studies Among these are to be mentioned the studies of *Jahnke et al (1958), Steel (1959 a, b),* Hartmann *et al* (1960), Jirgensons *et al* (1960), Kovacs & Daune (1961), Filitti-Wurmser & Hartmann (1962), Szabolcs *et al* (1965) and Wetter & Jahnke (1964), who all compare the intrinsic viscosities of isolated ,M-paraproteins with their other physicochemical and molecular parameters Unfortunately the authors express their results of the intrinsic viscosities in *different ways, which makes their comparison* difficult

Rheological properties of blood and plasma in MW and MM

In all the works cited the *purpose* of the determination of serum or plas*ma viscosity usually* aimed at the applying of serum viscosity as a clinical laboratory test or a correlative adjunct and not so much as a rheological subject of study Investigations in which the rheological properties of blood and plasma of patients with paraproteinemia have been *considered or studied*

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PURPOSE OF THE PRESENT STUDY

In the present study the approach to the problem aimed at the determination of the *viscosity of blood, plasma* and serum by a relatively simple, uniform method rather than at the exploration of the rheological behavior of blood and its components The author also tried to collect patient series large enough to permit some statistically confirmed conclusions

One of the main purposes of the study was to observe the viscosity values of whole blood, plasma and serum in patients exhibiting changes in different normal and pathological plasma proteins and to compare these results with the viscosities of samples from healthy control persons of comparable age Therefore, in addition to patients with multiple myeloma and macroglobulinemia, a series consisting of patients suffering from ankylosing spondylitis was included to serve as an example of severe dysproteinemia in which the alterations in plasma proteins in relation to the normal protein pattern are *only quantitative, not also* qualitative as in paraproteinemias

Secondly, the behavior of the viscosities at there temperatures were studied mainly in order to find out whether the characterization and even the differentiation of dys- and paraproteinemic samples from each other and from samples of the control series by *thermoviscometry* is possible

The third main object was to obtain a view of the usefulness of viscosity determinations in the evaluation of dys- and paraproteinemia For this purpose the viscosity values of blood, plasma and serum were compared with various hematological parameters, plasma protein fractions and results of some non-specific clinical laboratory *tests performed by commonly* used methods Particular attention in these correlation trials was paid to possible differences between the behavior of various paraproteins in order to obtain information on whether viscometry as one of the methods of protein studies can be used in the distinction and *characterization* of paraproteinemias

MATERIAL

PATIENTS

The study comprises samples from 30 patients with a diagnosis of **multiple myeloma** Two thirds of these cases were admitted during the period 1961—1965 to the I, II and III Departments of Medicine of the University of Helsinki, and the remainder were from the Departments of Medicine of Helsinki Municipal Hospitals The mean age of the patients was 59 years with a range of 30—75 years There were 17 male and 13 female patients

The diagnosis of multiple myeloma was based in addition to supportive history and clinical manifestations on the demonstration of typical myeloma cells in bone marrow smears on the presence of sharp M peaks which were visible in most cases in serum paper electrophoresis and on signs of osteolytic lesions or osteoporosis in X-ray In all cases the diagnosis was supported by a characteristic immunoelectrophoretic finding and in all except two patients also by serum ultracentrifugal analysis

The **macroglobulinemia** series consists of 17 patients eleven males and six females Their age ranged between 40 and 79 years the mean being 60 years. Five of them were from the I and II Departments of Medicine University of Helsinki, and seven cases from the Medical Clinic, University of Turku The remaining five patients were from the Hospital of the Wihuri Research Institute and from Helsinki Municipal Hospitals

The diagnosis of macroglobulinemia was based on the demonstration of pathologic (> 10 per cent) amounts of macroglobulins ($S_{20,w} > 15$) in the serum ultracentrifugation and on the finding of increased γM paraprotein in immunoelectrophoresis together with the supportive clinical picture The bone marrow revealed in most cases increased numbers of atypical lymphoid cells

Fourteen of the 17 cases with elevated macroglobulin levels were considered to represent Waldenstrom s macroglobulinemia, while in cases 6, 11 and 14 (see Appendix Individual values Table 10) the clinical picture was to such a degree nonconfirmative that the diagnosis of primary macroglobulinemia could not be made although no other cause for macroglobulinemia (Ritzmann *et al* 1960 b Phelps & Geokas 1963) was found

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METHODS

The blood samples from the patients and the control subjects were drawn early in the morning after overnight fasting and before the morning meal Minimal stasis was used before inserting a wide bore needle into the antecubital vein Without using tourniquet a blood sample of about 45 ml was allowed to run into six centrifuge tubes two of which were heparinized (about 7 units ml of blood) in order to yield blood and plasma samples two were unheparinized for the procurement of serum At the same time samples for plasma fibrinogen and for the erythrocyte sedimentation rate were taken The tubes containing anticoagulants were immediately corked and carefully shaken to mix the anticoagulants The tubes for serum were allowed to clot for about 1 2—1 hour and were centrifuged together with the other tubes for 30 min at 3 000 r p m at room temperature

Capillary blood samples for routine hematological studies were taken and treated by usual laboratory techniques

After centrifugation the plasma and serum samples were divided into several smaller samples and were stored at —10° C for some days or weeks before analysis

The routine hematological analyses and the determinations of the erythrocyte sedimentation rate, blood viscosity and clotting of fibrinogen to fibrin were performed on the same day

Hemoglobin concentration and blood cell counts

The blood hemoglobin values and red and white cell counts were for practical reasons determined at the laboratories of the hospitals where the patients were being treated In all the laboratories the cyanmethemoglobin method for hemoglobin determination was used and the results were expressed as grams per 100 ml

Hematocrit

The hematocrit values (vol per cent) were determined in duplicate from *wellmixed* heparinized venous samples by using van Allen hematocrit tubes. The tubes were centrifuged for 30 min at 3 000 r p m. The hematocrit values obtained have been used without correction for trapped plasma

The *ankylosing spondylitis* series includes 22 cases, 17 of which were from the Hospital of the Rheumatism Foundation, Heinola, and the remainder were from the I and II Departments of Medicine, University of Helsinki, and from the Department of Rheumatology, Kivela (Helsinki Municipal) Hospital Two of the patients were women The mean age of this series was 43 years and the range from 19 to 58 years

In the group of ankylosing spondylitis were only included patients with the classical clinical picture of the disease, in whom due to the long duration of the symptoms and to the severe clinical activity there was to be expected profound dysproteinemia in the blood As an estimate of this a recent erythrocyte sedimentation rate over 50 mm/h was used in the selection

All the patients except one had bilateral roentgenological changes in the sacroiliac joints, beginning from sacroilitis to erosions and sclerosis of the joint In about half of the patients osteoporosis of the vertebral bodies, paravertebral syndesmophytes and/or a bamboo spine were found in X-ray In five cases, in addition, erosions and osteoporosis of a minor degree also were noted in the peripheral joints One young male patient (Case 5) with unilateral sacroilitis and persistent symptoms of sacroiliac joint syndrome, elevated erythrocyte sedimentation rate, malaise and fever was considered to represent an incipient ankylosing spondylitis

The *Waaler-Rose test* was negative in all the patients

CONTROLS

Blood samples in the control series were taken from 24 apparently healthy persons ranging in age from 24 to 76 years The series was composed of 13 males and 11 females, and the mean age was 49 years Eleven of these control subjects were from the Kustaankartano Municipal Home for the Aged Helsinki, and were selected as control subjects in order to obtain about the same age grouping as in MM- and MW-series These in principle »healthy» aged subjects were picked out after checking of their clinical and laboratory records (see Appendix Control series, Table 12)

The criteria for the selection of control persons were a »normal» erythrocyte sedimentation rate (in females < 15 mm/h and in males < 10 mm/h) and hemoglobin concentration (13—16 g/100 ml for men and 12—15 g/100 ml for women) However, as can be seen from the individual data in the Appendix, in three subjects (all belonging to the advanced age group Cases 15, 23 and 24) these upper limits of the erythrocyte sedimentation rate were exceeded despite no obvious cause of disease for the elevation Knowing the tendency of the erythrocyte sedimentation rate to rise with advancing age (Bottiger & Molin 1964) these slight exceptions were allowed

The subjects in the control series had participated in the annual mass chest roentgenographic examination

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The determinations of the serum total protein content were made in duplicate by the biuret method described by Siltanen & Kekki (1960) In this method the color is stable and no standard curve is required, since the copper content of the color solution bears a linear relationship to the protein concentration of the solution

Plasma fibrinogen concentration

The amount of fibrinogen in the blood plasma was determined in duplicate by a method slightly modified by Punsar (1960) from the methods of Ratnoff & Menzie (1951) and Bidwell (1953)

Nomenclature — The term *fibrinogen* will be used to describe the component of plasma which is clotted by calcium chloride The term *fibrin* will refer to this clotted fibrinogen, as measured by the technique described Since other plasma proteins are known to be included in fibrin clots, the term *fibrin* will not be used to imply a purified protein Alkaline solutions of fibrin react with Folin & Ciocalteu's phenol reagent this property of fibrin will be referred to as its *tyrosine-like activity*

Clotting of fibrinogen to fibrin — About 2 5 ml of venous blood was allowed to run into a small (70 $\times$ 10 mm) siliconized glass tube containing the residue left after evaporating 0 5 ml of 3 8 per cent sodium citrate The sample was shaken until the anticoagulant was dissolved The plasma was separated by centrifugation for 30 minutes at 4 000 r p m

After centrifugation, 0 2 ml of plasma was pipetted into two similar siliconized tubes containing 0 4 ml of 0 334 per cent $CaCl_2$ solution and in which a thin glass rod was upright The clotting occurred at room temperature in about 20—30 minutes

After about one hour the fibrin clot was carefully wrapped around the rod, the serum was discarded, and the fibrin clot was squeezed against the walls of the siliconized tube The fibrin was then washed by filling the tube three times with ice cold saline (0 9 per cent) and three times with ice cold distilled water After each filling the squeezing of the clot was repeated and the tube was left standing for about 15 minutes Finally the rod with the fibrin clot was transferred into a clean 10 ml centrifuge tube, in which it was left to dry for a later analysis

Determination of the tyrosine-like activity of clotted fibrin —

Reagents

0 1 N NaOH, filtered before use

12 5 per cent (w/v) Na_2CO_3, filtered before use

0 01 M $CuSO_4$

Folin-Ciocalteu s phenol reagent, stored in the dark at 4° C

20 mg per cent tyrosine solution in 0 1 N HCl (stored at 4°C)

0 1 N HCl

Procedure — 2 0 ml of 0 1 N NaOH was added to each tube containing a glass rod with adherent dried fibrin clot The tubes were then immersed in a boiling water bath for two min-

utes, taking care that the warm NaOH came into contact with fibrin The evaporation was minimized with glass stoppers The tubes were cooled to room temperature and 6 0 ml of 12 5 per cent Na_2CO_3 was added to the mixture After placing a glass stirring rod into each tube, 1 ml of 0 01 M $CuSO_4$ was added and the content was stirred immediately with the rod. After 1—2 minutes simultaneously stirring 1 0 ml of Folin Ciocalteu s reagent was added

After 30—60 minutes the resulting blue color was read against the blank in a Beckman model B spectrophotometer at a wave length of 640 mμ using cuvettes with an internal diameter of 5 mm

The blank was prepared by exactly duplicating the procedure outlined, but without the fibrin clot

The tyrosine standard was prepared as follows Exactly 0 5 ml of the tyrosine solution was pipetted into two centrifuge tubes and 1 5 ml of NaOH was added after which the tubes were treated along with the fibrin tubes according to the procedure already described The resulting blue color was similar to that caused by the reaction of fibrin with the phenol reagent Its intensity was read against a blank which was prepared in the same way as the standard solution except that the tyrosine solution was substituted by 0 5 ml of 0 1 N hydrochloric acid

The color produced by the fibrin samples was compared with that of the tyrosine standard and was expressed in terms of μg of tyrosine obtained according to the formula,

$$\frac{X}{T} \cdot 100\ \mu g \text{ where}$$

X = reading for the fibrin sample
T = reading for the tyrosine standard.

Calculation of the fibrinogen concentration of plasma samples — A standard curve for determining the relationship between the calculated tyrosine like activity and the fibrinogen concentration of the plasma samples was constructed as follows The fibrinogen concentrations of six different plasmas were determined gravimetrically, and the tyrosine-like activity of samples of various volumes of these plasmas was estimated. Duplicate samples of 40 to 100 ml of citrated plasma were clotted with a double volume of 0 334 per cent $CaCl_2$ solution The fibrin of each sample was collected in the above described manner with the aid of a weighed glass rod and washed The fibrin adherent to the rod was left to dry at room temperature for some days after which the rod was put to dry in an exsiccator for several hours The weight of the rod and the fibrin together was then determined. The drying procedure was repeated on several days until a stable weight was reached Finally the weight of the glass rod alone was again measured and the amount of dry fibrin and the fibrinogen concentration of the plasma were then calculated. Several samples of 0 1 to 0 8 ml of the same plasmas were clotted with double amounts of $CaCl_2$ solution, washed and treated as described, and their tyrosine-like activity was determined

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After centrifugation, 0 2 ml of plasma was pipetted into two similar siliconized tubes containing 0 4 ml of 0 334 per cent $CaCl_2$ solution and in which *a thin glass* rod was upright The clotting occurred at room temperature in about 20—30 minutes

After about one hour the fibrin clot was carefully wrapped around the rod the serum was discarded, and the fibrin clot was squeezed against the walls of the siliconized tube The fibrin was then washed by filling the tube three times with ice cold saline (0 9 per cent) and three times with ice cold distilled water After each filling the squeezing of the clot was repeated and the tube was left standing for about 15 minutes *Finally the rod with the fibrin clot was* transferred into a clean 10 ml centrifuge tube, in which it was left to dry for a later analysis

Determination of the tyrosine-like activity of clotted fibrin —

Reagents

0 1 N NaOH, filtered before use

12 5 per cent (w v) Na_2CO_3, filtered before use

0 01 M $CuSO_4$

Folin-Ciocalteu s phenol reagent, stored in the dark at 4° C

20 mg per cent tyrosine solution in 0 1 N HCl (stored at 4°C)

0 1 N HCl

Procedure — 2 0 ml of 0 1 N NaOH was added to each tube containing *a glass rod* with adherent dried fibrin clot The tubes were then immersed in a boiling water bath for two min-

utes taking care that the warm NaOH came into contact with fibrin The evaporation was minimized with glass stoppers The tubes were cooled to room temperature and 6 0 ml of 12 5 per cent Na_2CO_3 was added to the mixture After placing a glass stirring rod into each tube 1 ml of 0 01 M $CuSO_4$ was added and the content was stirred immediately with the rod After 1—2 minutes simultaneously stirring 1 0 ml of Folin-Ciocalteu's reagent was added

After 30—60 minutes the resulting blue color was read against the blank in a Beckman model B spectrophotometer at a wave length of 640 $m\mu$, using cuvettes with an internal diameter of 5 mm

The blank was prepared by exactly duplicating the procedure outlined, but without the fibrin clot.

The tyrosine standard was prepared as follows Exactly 0 5 ml of the tyrosine solution was pipetted into two centrifuge tubes and 1 5 ml of NaOH was added, after which the tubes were treated along with the fibrin tubes according to the procedure already described. The resulting blue color was similar to that caused by the reaction of fibrin with the phenol reagent Its intensity was read against a blank which was prepared in the same way as the standard solution except that the tyrosine solution was substituted by 0 5 ml of 0 1 N hydrochloric acid

The color produced by the fibrin samples was compared with that of the tyrosine standard and was expressed in terms of μg of tyrosine obtained according to the formula,

$\frac{X}{T}$ 100 μg where

X = reading for the fibrin sample

T = reading for the tyrosine standard

Calculation of the fibrinogen concentration of plasma samples — A standard curve for determining the relationship between the calculated tyrosine-like activity and the fibrinogen concentration of the plasma samples was constructed as follows The fibrinogen concentrations of six different plasmas were determined gravimetrically, and the tyrosine-like activity of samples of various volumes of these plasmas was estimated. Duplicate samples of 40 to 100 ml of citrated plasma were clotted with a double volume of 0 334 per cent $CaCl_2$ solution The fibrin of each sample was collected in the above described manner with the aid of a weighed glass rod and washed The fibrin adherent to the rod was left to dry at room temperature for some days after which the rod was put to dry in an exsiccator for several hours The weight of the rod and the fibrin together was then determined The drying procedure was repeated on several days until a stable weight was reached Finally the weight of the glass rod alone was again measured and the amount of dry fibrin and the fibrinogen concentration of the plasma were then calculated. Several samples of 0 1 to 0 8 ml of the same plasmas were clotted with double amounts of CaCl solution washed and treated as described and their tyrosine like activity was determined

A curve was then constructed by plotting the amount of fibrin in the samples against their tyrosine-like activity By using this curve it was possible to determine the fibrinogen concentration of unknown plasma samples from their tyrosine-like activity

Erythrocyte sedimentation rate

was determined in duplicate by the Westergren method at room temperature Values for 15 min 30 min, 45 min and one-hour sedimentation were observed in every case of the dys- and paraproteinemia series

SIA (euglobulin) test

This screening test for the detection of increased amounts of euglobulin in a given serum was performed throughout the study of serum samples *The performance of the test and* the evaluation of the results was *essentially the same as described by* Laurell & Waldenstrom (1961)

Presence of cryoglobulins or cryofibrinogen

in serum and plasma samples was tested only qualitatively by allowing the samples to remain overnight at 4—5°C, after which they were observed for precipitation or gelification No attempt for quantitation by, for instance, cryocrit or other means was made in the cases in which the test was positive (designated as +)

Paper electrophoresis of serum proteins

The paper electrophoretic fractionations of the serum proteins were performed in duplicate by a slightly modified method of Grassmann & Hannig (1954) used in this laboratory

The runs were carried out on Whatman No 1 *paper strips in a barbital* buffer of pH 8 6 and ionic strength *of 0 06 After runs at 70—75 volts* for 17—18 hours at room temperature *the dried strips were dyed with amido* black stain After decolorization of the excess *dye* and *drying, the strips* were rendered transparent with a mixture of paraffin oil and *α-brom*-naphthalin and were then scanned *with a photometric recorder* (Extinktionsschreiber Zeiss II)

The following fractions were obtained albumin, α_1-, α_2-, β- and globulins The so-called »protein tail» fraction was noted in the manual construction of fractions but was not counted The relative percentages of fractions were then determined by planimetry The concentrations of protein fractions in g 100 ml were computed by multiplying the total protein content by percentages corresponding to each fraction

Immunoelectrophoresis of serum proteins

The *immunoelectrophoretic* analyses of serum *samples from patients* with multiple myeloma and macroglobulinemia were performed by P Vuopio, M D, at the Central Labora-

tory of the Finnish Red Cross Blood Transfusion Service, Helsinki

Immunoelectrophoresis was carried out in a LKB immunoelectrophoresis apparatus according to the micromethod of Scheidegger (1955) The antisera used were commercial polyvalent horse antisera No 306 419 and 223 from the Pasteur Institute, Paris The sera containing M-components were used either as such or in up to fivefold dilution in saline

Ultracentrifugation of serum proteins

The sedimentation analyses were performed by R Schakir, M S (Chem Eng), at the State Serum Institute Helsinki The preparation of serum specimens for the analysis and the interpretation of the results were performed according to the standard method described by Jahnke & Scholtan (1960) The runs were carried out with a Phywe AG air-driven analytical ultracentrifuge, model 1948, at 51 000 ±300 r p m

The sedimentation behavior of serum proteins was examined in the multiple myeloma series in all except two patients (Cases 3 and 4 in case 3 the analysis failed three times because of a disturbing precipitate and in case 4 the amount of serum was insufficient) Also in one case in the macroglobulinemia series (Case 7) the lack of serum inhibited the analysis but in an earlier analysis the patient s serum had shown three fractions of macroglobulins of $S_{20,w}$ values of 18 5 S 28 0 S and 41 0 S Other sera with macroglobulinemia were examined ultracentrifugally

Viscosity of blood, plasma and serum

At the time of planning of the present study no suitable viscometer was commercially available that would have fulfilled the requirements set both by the rheological properies of blood and by the special features of the samples examined. Already the rapid tendency of red cells to aggregate and settle in the blood samples of patients together with many practical and theoretical disadvantages (Wayland 1965 b) prevented the use of capillary viscometers operating by the force of gravity alone The author, therefore, constructed for his use a viscometer in which at least some of the most obvious drawbacks could be eliminated. It became evident that simultaneously or slightly later some other workers had arrived at the same basic solution of the principle of viscometer design (e g Copley *et al* 1960, Charm & Kurland 1962, Harkness 1963)

Design of the viscometer unit — The general arrangement of the viscometer unit is shown diagrammatically in fig 1 In principle the apparatus is glass capillary viscometer with externally applied pressure Two calibrated pyrex glass capillaries AB with inner diameters of 0 65 mm and of 0 51 mm and respective lengths of 325 mm and of 255 mm (approximately 500 × diameters) were fused at each end onto wider side tubes AC and BD of 0.3 mm diameter These side tubes were graduated to 1 0 ml capacity with a scale of 0 1 ml This range of dimensions was chosen as

A curve was then constructed by plotting the amount of fibrin in the samples against their tyrosine-like activity. By using this curve it was possible to determine the fibrinogen concentration of unknown plasma samples from their tyrosine-like activity.

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The runs were carried out on Whatman No. 1 paper strips in a barbital buffer of pH 8.6 and ionic strength of 0.06. After runs at 70—75 volts for 17—18 hours at room temperature the dried strips were dyed with amido black stain. After decolorization of the excess dye and drying, the strips were rendered transparent with a mixture of paraffin oil and *α* brom naphthalin and were then scanned with a photometric recorder (Extinktionsschreiber Zeiss II).

The following fractions were obtained: albumin, α_1-, α_2-, β- and γ-globulins. The so-called »protein tail» fraction was noted in the manual construction of fractions but was not counted. The relative percentages of fractions were then determined by planimetry. The concentrations of protein fractions in g/100 ml were computed by multiplying the total protein content by percentages corresponding to each fraction.

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sec for the advancig meniscus to move between the two marks in the side tube indicating a calibrated volume of 1 0 ml By only handling the valves in the pressure system several experiments could be done with the same sample in both directions during a short time Usually two flow times were measured in each direction and a mean was taken for calculations

The flow times of the blood, plasma and serum samples were determined in this manner at the temperatures of 10°, 20° and 37°C with the two capillaries of 0 65 mm and 0 51 mm internal diameter using pressures of 50 and 100 mm Hg

The viscometers were cleaned carefully with distilled water after each sample and with ethanol-ether mixture between samples from different patients Periodically chromic acid solution was left overnight in the instruments After the washing procedure the capillaries were dried by powerful suction

Calibration and accuracy of the method — The viscometers were calibrated by measuring the flow times of distilled water at the same temperatures and with the same pressures as the test samples The means of 20 consecutive determinations of flow times for water, ranging from 10 to 30 seconds according to circumstances, were used in the calculations

The accuracy of the method was determined by calculating the standard error of the mean for the flow times of the blood plasma and serum samples This error was calculated for the samples of the myeloma group, which showed great variations in flow times and marked erythrocyte aggregation, thus well representing pathological specimens, and for the samples of the control series, in which the flow times were within rather small ranges and in which no clearly observable aggregation tendency during determinations was noted. The results of calculations of the standard error of the mean flow times are presented in table 3

Table 3 STANDARD ERROR OF THE MEAN OF FLOW TIMES IN WHOLE BLOOD PLASMA AND SERUM VISCOSITY DETERMINATIONS

	Blood	Plasma	Serum
Multiple myeloma			
Range sec	0 048—0 460	0 025—0 168	0—0 156
Mean of the group sec.	0 133	0 058	0 061
S D sec	0 102	0 033	0 042
Per cent of the mean flow time of the group	0.55	0 42	0.51
Controls			
Range sec	0—0 186	0—0 099	0 025—0 155
Mean of the group sec.	0 110	0 050	0 045
S.D., sec	0 056	0 019	0 032
Per cent of the mean flow time of the group	0 60	0 66	0.69

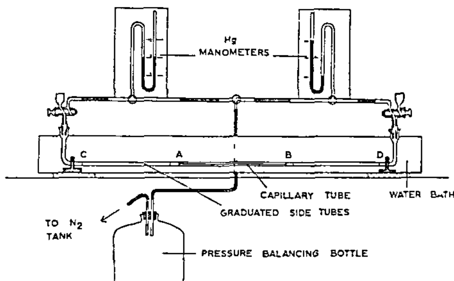

Fig 1 Diagram showing the viscometer used in the study

convenient in regard to the pressures, the varying nature of samples and the other conditions used, as well as with attention to the dimensional considerations stated by, e g, Green (1944), Bayliss (1952), Copley *et al* (1960)

The side tubes terminated in vertical ground glass sockets, which also served as filling and outlet reservoirs for the fluids to be tested. The side tubes were joined with the glass parts from the pressure system (see Fig 1)

The pressure system consisted of a nitrogen gas tank connected with rubber tubes to a 10-liter pressure (balancing) bottle, which in turn was joined via a two-way tap to two identical mercury manometers The reservoir was so large that the small displacement during the flow of the fluid in the viscometer did not cause a noticeable fall in pressure The viscometer was immersed horizontally in a water bath and the temperature was controlled by an automatic pump thermostat within 0 2°C

Procedure — The total volume of sample required in the viscometer was approximately 1 5 ml The sample was poured into either of the glass sockets at the end of the wider side tubes and was allowed to flow freely to the horizontal part of the side tube For the sake of uniformity and especially in order to minimize the resistance of the dried glass surfaces of the capillaries (the so-called wall adherence Copley *et al* 1960) the sample was at the beginning of each experiment pushed through the capillary and the opposite side tube which thus became wetted with the fluid to be tested After the pressure had been balanced accurately the valves were appropriately opened so that the applied balanced pressure pushed the fluid through the capillary Time(t) was taken with a stop-watch to 0 1

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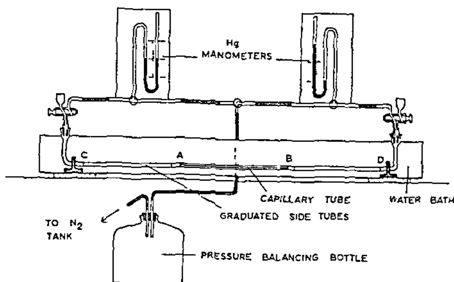
	Blood	Plasma	Serum
Multiple myeloma			
Range sec.	0 048—0 460	0 025—0.168	0—0 156
Mean of the group sec.	0 133	0 058	0.061
S.D., sec	0 102	0 033	0 042
Per cent of the mean flow time of the group	0.55	0 42	0.51
Controls			
Range sec	0—0.186	0—0 099	0 025—0 155
Mean of the group sec.	0 110	0 050	0 045
S.D., sec	0 056	0 019	0 032
Per cent of the mean flow time of the group	0 60	0 66	0.69



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RESULTS

HEMATOLOGICAL DATA AND PLASMA PROTEIN PATTERNS OF PATIENTS AND CONTROL SUBJECTS

The group data on hematological findings and plasma protein patterns in the patients with multiple myeloma macroglobulinemia and ankylosing spondylitis and in the control series are given in tables 5 6 and 7 The individual values obtained in the studies performed and the results of the viscosity measurements are compiled in tables 8—12 in the Appendix.

Hematological data

Table 5 presents the mean values standard deviations and ranges of hematological data in the patient and in the control series

Patients suffering from multiple myeloma were slightly more anemic than patients with macroglobulinemia Macroglobulinemia patients on the other hand had a lower mean value and wider ranges for hemoglobin red cell count and hematocrit than patients of the ankylosing spondylitis series The mean values for the mean corpuscular hemoglobin and for leucocyte counts were within normal limits in all the series

The mean erythrocyte sedimentation rate was highest (137 5 mm h) in the group of eight patients with A myeloma and lowest (76 0 mm h) in the small group of five patients with μ myeloma while it was of about the same order (113 1 and 113 0 mm h) in the groups of γG-myeloma patients and of patients with macroglobulinemia both consisting of 17 patients The mean erythrocyte sedimentation rate was 113 4 mm h for the entire myeloma series, and respectively 75 9 mm h for the patients in the ankylosing spondylitis series

Plasma protein patterns

The group means standard deviations and ranges of various biochemical and physicochemical serum protein analyses are presented in tables 6 and 7 where also the statistical significances (marked with asterisks) of series means in comparison to the respective mean value of the control series are noted.

As anticipated the mean values of the patient series mostly differed in regard to the principal protein frac-

Table 4 DEFINITIONS AND SYMBOLS OF VISCOSITY TERMS

Name	Symbol	Formula
Solution viscosity	η	
Solvent viscosity *	η	
Relative viscosity	η_{rel}	η/η_0
Specific viscosity	η_{sp}	$\eta-\eta_0/\eta_0 = \eta_{rel}-1$
Reduced specific viscosity	η_{sp}/c	$\eta-\eta_0/\eta_0/c = \eta_{rel}-1/c$

* Solvent viscosity = viscosity of distilled water = 1 0
c = protein concentration g/100 ml

Calculations and symbols of viscosity terms — In table 4 are listed the conventional names, symbols and formulas of the viscosity terms which were used in this work and with which the calculations of viscosities were performed

Statistical methods

Standard methods as outlined by *Croxton (1959)* were used for the statistical analyses of the results The statistical significances were determined by the t-test and correlations were studied usually by means of linear regression analysis

In some cases a non-linear model was found to be most suitable for the estimation of the relation between two variables as judged from the preliminary graphic consideration

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also was significant in the mean total protein concentration ($P < 0.01$) and in the mean $\gamma + M$ fractions ($P < 0.05$). On the other hand differences in these mean values between the entire myeloma and macroglobulinemia series and between the G- and γA groups of myeloma did not reveal any significance.

Significant differences ($P < 0.001$) were established between the means of G- and M fractions in the serum ultracentrifugal patterns of the myeloma and macroglobulinemia series whereas in regard to the A fraction the difference was slightly weaker ($P < 0.01$).

Patients with ankylosing spondylitis had on the average the highest levels of plasma *fibrinogen*, the mean of the series being 593.3 ± 103.8 (S.D.) mg/100 ml and the values ranging between 473 and 844 mg/100 ml. The difference of the spondylitis mean from that of the control series (297.3 ± 59.4, range 182—410 mg/100 ml) was significant ($P < 0.001$). The same was true for the means of the myeloma series (mean 417.2 ± 116.5, range 194—634 mg/100 ml, $P < 0.001$) and of the macroglobulinemia series (mean 414.3 ± 148.3, range 250—836 mg/100 ml), but in the latter the significance between means was less distinct ($P < 0.01$).

The SIA (euglobulin) test was positive in 15 of the 17 sera (88 per cent) from macroglobulinemia patients (see Appendix, Table 10) and in four sera from the 17 (24 per cent) patients with γG myeloma (Appendix, Table 8). In sera of seven patients with ankylosing spondylitis the test was very weakly positive designated as +. In all control sera the test was negative.

ELECTROPHORETIC DISTRIBUTIONS OF SERUM PROTEINS

concentrations (g/100 ml) electrophoretic distribution α_1 globulin	α_2-globulin	β globulin	γ(+M) globulin
0.27 ± 0.06 0.18—0.35	0.59 ± 0.13 0.37—0.92	0.88 ± 0.13 0.66—1.16	1.42 ± 0.24 1.03—1.75
0.40 ± 0.11 ** 0.24—0.70	0.83 ± 0.15 * 0.64—1.17	1.07 ± 0.11** 0.84—1.26	2.24 ± 0.39 ** 0.89—4.18
0.35 ± 0.09 0.20—0.53	0.67 ± 0.20 0.15—1.10	0.94 ± 0.74 0.45—3.34	3.97 ± 2.47*** 0.39—8.46
0.32 ± 0.08 0.20—0.50	0.63 ± 0.22 0.1[illegible]—0.96	0.64 ± 0.17 0.45—0.92	4.96 ± 2.14 1.40—8.46
0.36 ± 0.08 0.27—0.46	0.69 ± 0.13 0.55—0.92	1.51 ± 1.09 0.65—3.34	3.67 ± 2.52 0.39—6.65
0.40 ± 0.10 0.25—0.[illegible]3	0.76 ± 0.22 0.53—1.10	1.06 ± 0.19 0.45—2.58	1.11 ± 0.63 0.44—2.12
0.35 ± 0.09* 0.21—0.50	0.69 ± 0.20 0.47—1.25	0.71 ± 0.15** 0.45—1.03	3.65 ± 1.61*** 2.02—8.01

Table 5 HEMATOLOGICAL DATA.

		Control *subjects*	Ankylosing *spondylitis*	Multiple *myeloma*	Macroglobulinemia
Hemoglobin g/100 ml	Mean±SD Range	14.0±1.1 *12.4—15.7*	12.3±1.2 *9.4—14.0*	10.1±2.0 *6.0—13.9*	11.2±2.0 *7.8—15.6*
Red cell count millions/cu mm	Mean±SD Range	4.84±0.37 4.29—5.60	4.34±0.12 3.30—4.90	3.27±0.73 1.66—4.50	3.75±0.72 2.30—4.90
Mean corpuscular hemoglobin, *μμg*	Mean±SD Range	28.8±1.2 27.0—30.5	28.5±2.77 24.5—32.0	31.2±3.5 25.0—40.0	29.8±2.4 26.0—35.0
Hematocrit, %	Mean±SD Range	44.7±3.4 *37.5—50.0*	38.9±5.1 *29.5—47.0*	32.1±7.0 *24.0—44.0*	35.6±6.4 25.0—48.5
White cell count thousands/cu.mm	Mean±SD Range	5 900±1 430 4 100—9 700	7 000±1 890 5 200—13 000	5 800±3 090 1 200—15 200	6 050±2 450 1 400—11 600
Erythrocyte sedimentation rate mm/h	Mean±SD Range	9.0±4.2 3—20	75.9±25.9 39—124	113.4±37.7 24—160	113.0±29.5 45—152

tions significantly from those of the control series In addition, the mean serum total protein concentration and the mean paper electrophoretic γ+M-fraction in the small group of γμ-myeloma patients differed *significantly* (P < 0.001) from the respective values in the γG-myeloma group and the macroglobulinemia series, the difference from the γA-myeloma group

Table 6 SERUM TOTAL PROTEIN CONCENTRATIONS AND PAPER

Category			Serum total *protein conc*	Protein Paper Albumin
Control subjects	24	Mean±SD Range	7.57±0.39 6.8—8.3	4.41±0.35 3.80—5.37
Ankylosing spondylitis	22	Mean±SD Range	8.28±0.49*** 7.2—9.4	3.68±0.48*** 2.46—4.30
Multiple myeloma	*30*	Mean±SD Range	8.96±1.75*** 6.0—12.3	3.05±0.78*** 1.39—4.61
γG	17	Mean±SD Range	*9.47±1.72* 6.3—12.3	*2.91±0.75* *1.39—4.08*
γA	8	Mean±SD Range	9.16±1.32 7.7—11.5	3.02±0.80 2.12—4.34
γμ	5	Mean±SD Range	6.88±0.81 6.0—8.1	3.57±0.77 *2.54—4.61*
Macroglobulinemia	17	Range Mean±SD	8.84±1.17*** 7.4—11.8	3.44±0.54*** 2.18—4.22

*** P < 0.001 * P < 0.05

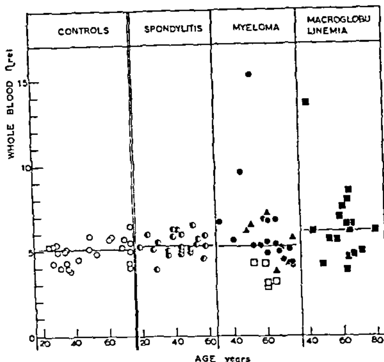


Fig 2 Whole blood relative viscosity in control series and in patients with dys- and paraproteinemia The individual values are plotted according to age Horizontal lines = median values

○ = control subjects
◐ = patients with ankylosing spondylitis
● = patients with γG-myeloma
▲ = patients with γA-myeloma
□ = patients with γμ-myeloma
■ = patients with macroglobulinemia

those of the latter series Notably the five cases with γμ myeloma showed the lowest blood viscosity values of the paraproteinemia series The age of the control subjects did not appear to influence their relative blood viscosity as determined by the present method

Plasma viscosity

The medians and individual values of plasma relative viscosity grouped according to patients' age in the different series are presented in fig 3 The ranges of plasma relative viscosity in the multiple myeloma (1 95—8 25) and in the macroglobulinemia series

Table 7 FRACTIONS IN SERUM ULTRACENTRIFUGAL ANALYSIS

			Protein concentrations (g/100 ml)				
ategory			X (< 4S)	A (4 5 S)	G (7 S)	Z (9—13 S)	M (> 15 S)
ultiple myeloma	28	Mean ± S D	0 58 ± 0 28	3 65 ± 1 00**	3 96 ± 2 41***	0 44 ± 0 85	0 15 ± 0 13***
		Range	0—1 1	1 5—5 6	0 7—9 6	0—2 8	0—0 4
γ G	15	Mean ± S D	0 55 ± 0 27	3 34 ± 1 05	5 13 ± 2.37		0 15 ± 0 13
		Range	0 1—1 0	1 5—5 1	1 9—9 6		0—0 4
γ A	8	Mean ± S D	0 50 ± 0 30	3 64 ± 0 70	3 44 ± 1 67	1 48 ± 1 02	0 10 ± 0 05
		Range	0—0 9	2 5—4 9	1 8—6 9	0—2 8	0—0 4
μ	5	Mean ± S D	0 76 ± 0.24	4 60 ± 0 07	1 30 ± 0 42		0.24 ± 0 09
		Range	0 5—1 1	3 7—5 3	0 9—1 8		0 1—0 4
Iacroglobulinemia	16	Mean ± S D	0 54 ± 0 18	4 47 ± 0 75	1 77 ± 1 14		2 05 ± 1.20
		Range	0.3—1 1	2 7—5 6	0 7—5 7		0 8—5 6

* P < 0 001 ** P < 0 01

RESULTS OF BLOOD, PLASMA AND SERUM VISCOSITY MEASUREMENTS

The values to be compared in the following are the results of viscosity measurements at 37°C with the capillary of 0 65 mm bore and 325 mm length using 100 mm Hg pressure as driving head The results obtained under these test conditions were selected for comparison because of the uniformity of the conditions and in order to avoid the possible influence of the temperature sensitivity of the different samples on the whole blood, plasma and serum relative viscosities If not specially stated, these viscosity values of the conditions mentioned are used in the comparisons with other data throughout of this study

Blood viscosity

Fig 2 shows the medians and ranges of whole blood relative viscosity in the patient and in the control series The individual blood viscosity values are plotted according to the age of the patients

Despite the wide range of blood viscosity in regard to upper limits in the myeloma and the macroglobulinemia series the majority of the values of these series fell well within the range limits in the control and ankylosing spondylitis series Also, the medians of the myeloma and the macroglobulinemia series did not differ clearly from

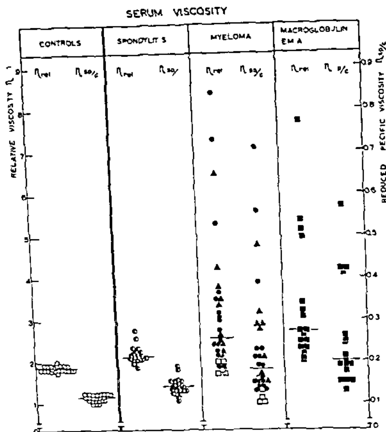


Fig 4 Serum relative viscosity (left columns) and serum reduced specific viscosity (right columns) in control and patient series Horizontal lines = median values Symbols as in fig 2

and as reduced specific viscosity ($\eta_{sp/c}$ right columns) in the various series

Again patients with paraproteinemia showed manifold ranges of serum viscosities as compared with the rather compact distribution of the respective values in the control series and in the dysproteinemic patients with ankylosing spondylitis Judging from the median levels in the last mentioned series there was a clear difference from the controls On the other hand no distinct difference in medians was found between the myeloma and the macroglobulinemia series Like the blood and plasma viscosity, the serum viscosity was lowest in the five patients with paraproteinemia Thus their mean

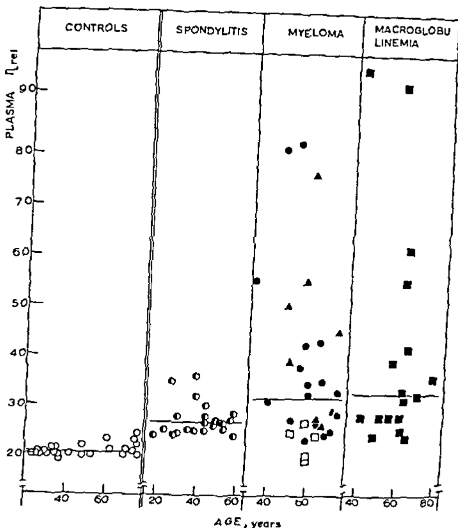


Fig 3 Plasma relative viscosity in control series and in patients with dys- and paraproteinemia The individual values are plotted according to age Horizontal lines = median values Symbols as in fig 2

(2 38—9 52) were markedly wider than that of spondylitis series (2 38—3 59) Likewise the medians in these paraproteinemia series were clearly higher than those in the ankylosing spondylitis and the control series the latter two also showed a distinct mutual difference with respect to the range and the median value of plasma viscosity A slight tendency of plasma viscosity to rise with increasing age could be observed in the controls, but due to small number of test persons no statistical analysis was attempted

The mean plasma relative viscosity in the control series, 2 09 ± 0 13 (S D), was practically the same as the mean value (2 12 ± 0 29) for , μ-myelomas

Serum viscosity

Fig 4 presents the serum viscosity values and medians expressed as relative viscosity (η_{rel}, left columns)

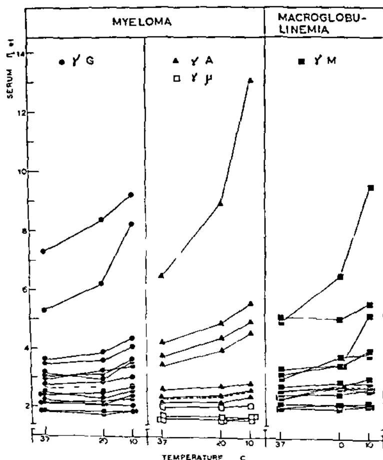


Fig 5 Temperature induced changes in serum relative viscosity in cases of myeloma and macroglobulinemia (with the exception of cases of cryoglobulinemia) Dotted lines = median values Symbols as in fig 2

Viscosities in the sera of control and spondylitis series were practically unchanged or exhibited only a slight increase with falling temperature, as did also the paraproteinemic sera with the relative viscosity at 37°C below the value of 3 units When in the latter series this viscosity value at 37° was exceeded the temperature dependence of serum viscosity usually was the steeper the higher the initial viscosity value at this temperature The sera containing cryogelglobulins showed clearly greatest temperature sensivity of the viscosity whereas the fourth serum with precipitating cryoproteins did not readily differ in its viscosity behavior from the sera of the γA group (Fig 6)

In fig 7 the same results as in former figures are expressed in a different manner in a form of temperature —

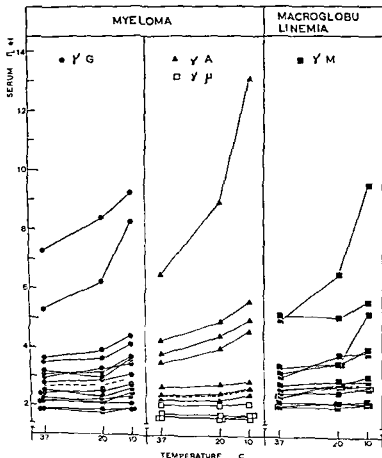
serum relative viscosity value, 1 83 ± 0 19 (S D), was almost the same as the mean value in the control series, 1 86 ± 0 08

A closer inspection of the individual viscosity values (Tables 8—12) reveals that, for instance, in the γG-myeloma group *the first three values of reduced specific viscosity*, like the respective viscosities of the first patients in the γA and γM groups, clearly differed from the average values of the group *On the contrary*, the ankylosing spondylitis series and the controls showed an even distribution of $\eta_{p/c}$

TEMPERATURE SENSITIVITY OF DYS- AND PARAPROTEINEMIC SERA AND *ITS EFFECT ON VISCOSITY VALUES*

Cryoglobulins were present in four paraproteinemic sera In two cases (Cases 1 and 2) of the macroglobulinemia series and in one case (Case 1) of the γG-myeloma group (see Appendix, *Tables 8—10*) *the serum samples* gelified at 4°C overnight, while in a case (Case 22) of the γA-myelomas the pathological protein formed a precipitate in cold All the mentioned sera, however, dissolved within few minutes when heated to 37°C None of the an*kylosing spondylitis sera or control sera* showed this cryosensitivity Neither cryofibrinogen was found in any of the plasma samples of the patient or control series, although some of the plasma samples in the ankylosing spondylitis series in particular exhibited a *slight tendency to flocculate on cooling* This phenomenon, however, was interpreted to be due to the presence of heparin, *which* was used as anticoagulant and which is known to be capable of precipitating the fibrinogen in cold (Heinrich *et al* 1963)

The results of the *viscosity measurements* at three temperatures (10°, 20° and 37°C) *are to be found in the viscosity* tables in the Appendix From them it is obvious that the blood, plasma and *serum viscosities showed* in principle a similar response to measurements at various temperatures, although understandable deviations due to different concentrations and qualities of the cellular and protein components were observed As an example and *because the factors determining* the temperature response of viscosities evidently exist in sera, the temperature motivated behavior of *serum* relative viscosity in cases of paraproteinemia is presented in fig 5 with the exception of viscosity changes *of sera containing* cryoglobulins, which are shown by fig 6 As a reference the ranges of the respective temperature-*induced* response of viscosity in the control ankylosing spondylitis and macroglobulinemia series were *also included in the latter figure*



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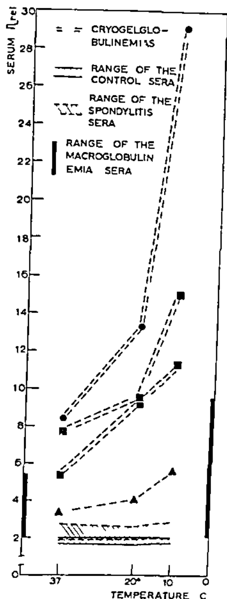


Fig 6 Temperature induced changes in serum relative viscosity in four cases of paraproteinemia in which cryoglobulins were found in the serum Symbols as in fig 2

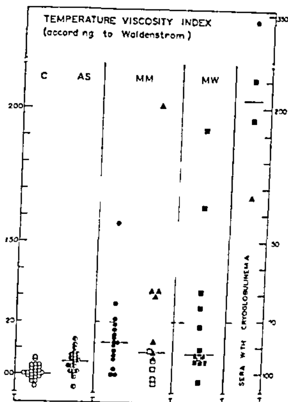


Fig 7 Temperature — viscosity index (TVI) in control subjects and in patients with ankylosing spondylitis, multiple myeloma and macroglobulinemia The TVI values of sera containing cryoglobulins are shown in their own column Horizontal lines = median values Symbols as in fig 2

viscosity index Many of the myeloma sera especially those of the A-variety showed temperature — viscosity index values greater than 120 and 10 of the 15 sera containing macroglobulins without cryoglobulins remained below this index limit the exceeding of which has earlier been considered char-

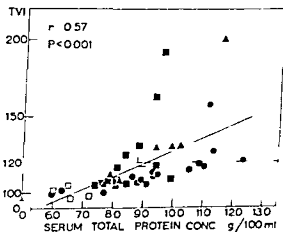


Fig 8 Relationship between temperature — viscosity index and serum total protein concentration in cases of paraproteinemia with the exception of cryoglobulinemia Regression equation $y = 42.7 + 8.524x \pm 18.9$ Symbols as in fig 2

acteristic of macroglobulinemia None of the sera having a temperature — viscosity index value of more than 120 contained paraprotein of 10 g/100 ml, although the serum total protein content in myeloma sera displaying this marked cryosensitivity of viscosity surpassed the mentioned value In macroglobulinemia sera with lower total protein values were capable of causing a similar response of viscosity on cooling

Although there seems to exist a significant relationship between the temperature — viscosity index and the serum total protein concentration (Fig 8) the scatter of the data in this figure also points to qualitative differences in the paraproteins of different patients

CORRELATIONS OF HEMATOLOGICAL AND PLASMA PROTEIN DATA TO VISCOSITY VALUES

Correlations of blood viscosity to hemoglobin concentrations and hematocrit values

Due to the small number of correlative trials between hematological data and whole blood viscosity in dys- and especially in paraproteinemias some principal relationships between them were examined and the results were compared with the respective relations in the control series

Hemoglobin concentration and hematocrit value — While significant correlations were noted in the control series between blood relative viscosity and hemoglobin ($r = 0\,78$ $P < 0\,001$ $y = 1\,748 + 0\,485x \pm 0\,430$) and relative viscosity and hematocrit (Fig 9) in ankylosing spondylitis patients the respective comparisons gave clearly weaker correlations ($r = 0\,44$ $P < 0\,05$) In patients with multiple myeloma and macroglobulinemia the relationships of these hematological parameters to whole blood viscosity were insignificant

However, if instead of the whole blood viscosity alone the ratio $\frac{\text{Blood}\,\eta_{rel}}{\text{Plasma}\,\eta_{rel}}$ was used in these comparisons, the paraproteinemia series (Fig 10) and the controls series (Fig 11) showed good correlations in for instance hematocrit whereas in the spondyl-

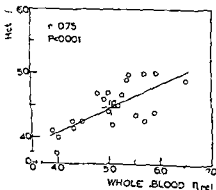


Fig 9 Relationship between hematocrit and whole blood *relative* viscosity in control subjects Regression equation $y = 25.6 + 3\,785x \pm 2.24$ Symbols as in fig 2

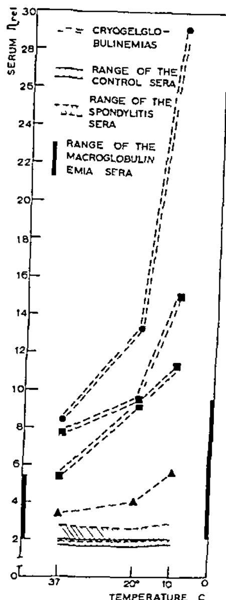
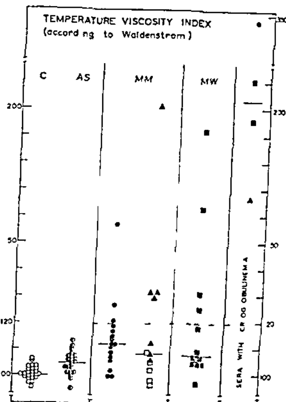


Fig 6 Temperature-induced changes in serum relative viscosity in four cases of paraproteinemia in which cryoglobulins were found in the serum Symbols as in fig 2



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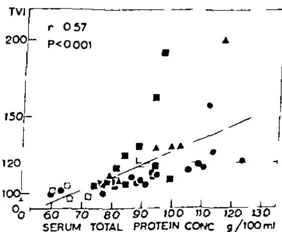

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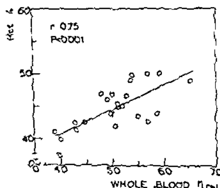

Fig 9 Relationship between hematocrit and whole blood relative viscosity in control subjects Regression equation $y = 25.8 + 3.78x \pm 2.24$ Symbols as in fig 2

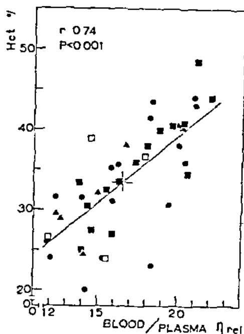

Fig 10 Relationship between hematocrit and the ratio $\frac{\text{Blood } \eta_{rel}}{\text{Plasma } \eta_{rel}}$ *in cases of paraproteinemia* Regression equation $y = 5.89 + 16.73x \pm 4.78$ Symbols as in fig 2

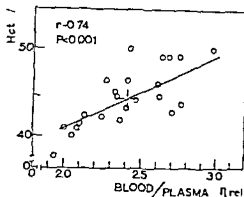

Fig 11 Relationship between hematocrit and the ratio $\frac{\text{Blood } \eta_{rel}}{\text{Plasma } \eta_{rel}}$ in control subjects. Regression equation $y = 22.8 + 9.137x \pm 2.30$

itis series the relationships between this ratio and hematocrit ($r = 0.34$) and hemoglobin ($r = 0.40$) were not significant

Correlations of plasma viscosity to erythrocyte sedimentation rate and *plasma fibrinogen concentration*

Erythrocyte sedimentation rate — Correlations of plasma viscosity (at 20°C with 100 mm Hg pressure and capillary with 0 65 mm bore) to the one-hour erythrocyte sedimentation rate in the control subjects and the ankylosing spondylitis series are illustrated in fig 12 The relationships were significant with correlation coefficients of about the same order in both groups In cases with paraproteinemia no linear correlation between these parameters could be found because of the rapid sedimentation of red cell aggregates Neither 15- nor 30-minute sedimentation rates, which were noted in every case in *the multiple myeloma* and macroglobulinemia series, revealed any linear relationship between values for plasma relative viscosity and erythrocyte sedimentation rate

Plasma fibrinogen concentration — If plasma and serum relative viscosities are determined, the difference between these values should be able to indicate the amount of fibrinogen in the plasma This »viscosimetric determination of fibrinogen (equivalent to the specific viscosity of fibrinogen) was found indeed, *to show a very good correlation* ($r = 0.88$) to chemically determined fibrinogen in the controls and in the

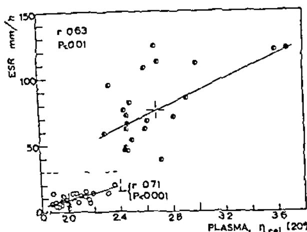

Fig 12 Relationship between one-hour erythrocyte sedimentation rate and plasma viscosity at 20 C in control (small rectangle) and ankylosing spondylitis series Regression equation for the control series $y = -38.5 + 23.14x \pm 3.04$ and for the spondylitis series $y = -47.9 + 46.13x \pm 20.6$

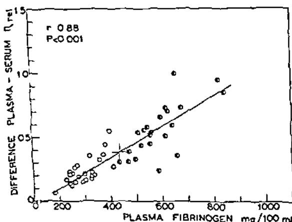

Fig 13 Relationship between plasma fibrinogen concentration and difference between plasma and serum relative viscosities (equivalent to viscometrically determined plasma fibrinogen) in control and ankylosing spondylitis series Regression equation $y = -0.138 + 0.00119x \pm 0.111$ Symbols as in fig 2

ankylosing spondylitis series (Fig 13) On the other hand in cases of para proteinemia the relationship was clearly weaker (Fig 14), obviously due to methodical errors which will be discussed later

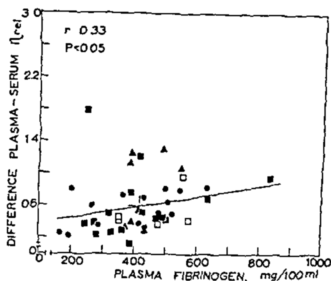

Fig 14 Relationship between plasma fibrinogen concentration and difference between plasma and serum relative viscosities in cases of paraproteinemia Regression equation $y = 0.330 + 0.000668x \pm 0.25$ Symbols as in fig 2

Correlations of serum viscosity to results of serum protein studies

In the following part data are given only on those comparisons that on the basis of a preliminary graphic consideration seemed to yield a significant correlation between the parameters under comparison

Serum total protein concentration — Linear regression analysis of the relations between serum total protein content and serum relative viscosity disclosed a significant positive correlation in the control and ankylosing spondylitis series (Fig 15)

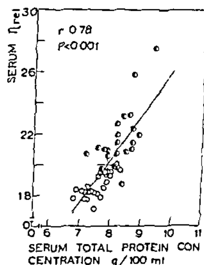

Fig 15 Relationship between serum total protein concentration and serum relative viscosity in control and ankylosing spondylitis series *Regression equation* $y = -0.251 + 0.286x \pm 0.133$ Symbols as in fig 2

A preliminary graphic consideration showed that in cases with paraproteinemia the same relationship was best fitted by the second degree parabola By this non-linear regression analysis a significant correlation was obtained between *total protein concentration* and serum relative viscosity also in myeloma and macroglobulinemia (Fig 16) The regression line of the control *series is shown in the* small rectangle inserted in this figure

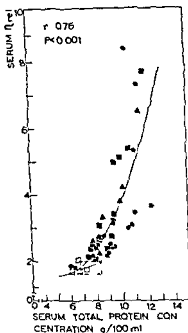

Fig 16 Relationship between serum total protein concentration and serum relative viscosity in cases of paraproteinemia The small rectangle shows the ranges of values in control series and the line within it represents the regression line of the linear correlation between these parameters in the control series Regression equation $y = 3.43 - 0.860x + 0.0907x$ Symbols as in fig 2.

A closer inspection of the results in the various groups in this graph showed however that in fact the majority of cases of G myeloma with the exception of three cases with extremely high serum viscosity values in relation to the protein concentrations had lower viscosities with a linear correlation to serum total protein concentration than cases with γA- or γM paraproteinemia at the respective concentrations Moreover the latter cases seemed to exhibit a non linear correlation For this reason a separate linear regression analysis between viscosity and total protein was performed for the cases of γG myeloma and ankylosing spondylitis and the control series all showing linear correlations This analysis showed a significant relationship ($r = 0.70$ $P < 0.001$ $y = -2.817 + 0.627x \pm 0.805$) despite the inclusion of the diverging three cases of G myeloma mentioned When the cases of macroglobulinemia and γA-myeloma and the control series were tested in the same manner by non-linear regression analysis a remarkably good correlation was found ($r = 0.96$ $P < 0.001$ $y = 8.377 - 2.229x + 0.183x$)

Paper electrophoretic α_2-fraction — Only in the control and the ankylosing spondylitis series was a significant linear positive correlation found between the serum relative viscosity and the α_2-fraction in paper electrophoresis (Fig 17) In the cases with paraproteinemia a weaker negative relationship was obtained between the respective data ($r = -0.45$, $P < 0.002$ $y = 5.71 - 3.691x \pm 1.47$)

Paper electrophoretic (+ M) -fraction — Significant relationships between serum relative viscosity and γ-fraction in paper electrophoresis were observed in the control and the spondylitis series (Fig 18) In cases with paraproteinemia for which no figure is shown the correlation coefficient was still better ($r = 0.84$, $P < 0.001$ $y = 0.515 + 0.676x \pm 0.907$) Because of the difficulty to accurately distinguish normal γ-globulin from the paraprotein fraction in paper electrophoresis the sum of these two frac

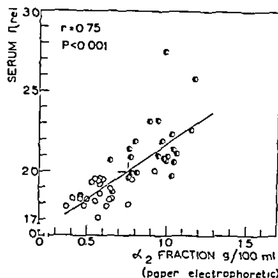

Fig 17 Relationship between paper electrophoretic α_2-globulin and serum relative viscosity in control and ankylosing spondylitis series Regression equation $y = 1.47 + 0.710x \pm 0.141$ Symbols as in fig 2

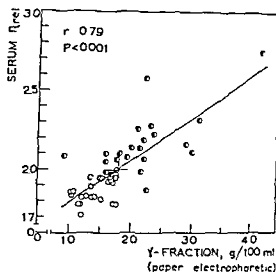

Fig 18 Relationship between paper electrophoretic γ-globulin and serum relative viscosity in control and ankylosing spondylitis series Regression equation $y = 1.54 + 0.264x \pm 0.133$ Symbols as in fig 2

tions has been used in the calculations throughout this study

If instead of the serum relative viscosity, the paper electrophoretic γ + M-fractions in the γG- and γA-myeloma groups and the macroglobulinemia series are plotted against the serum reduced specific viscosity, a better characterization between the various paraprotein properties and their amounts is obtained, as shown by figs 19 and 20 It is evident from fig 19 that, in principle, the correlation of the γG-paraprotein concentration to the serum reduced specific viscosity would have been non-linear in this material However, the departure from linearity evidently is caused by changes in the physicochemical milieu in the solution due to the increased molecular density because of the elevated total protein concentration Thus, the departing part of the curve

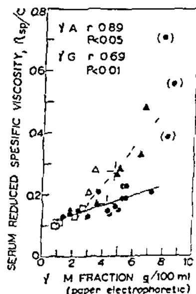

Fig 19 Relationship between paper electrophoretic γ + M-globulin and serum reduced specific viscosity in cases of γG- and γA-myeloma The values exceeding the electrophoretic protein concentration of 7.5 g/100 ml and the two cases of γA-myeloma (shown as white triangles) have been excluded for the reasons discussed in the text from the regression analyses The same is true for the cases of γμ-myeloma Regression equation for γG-myeloma $y = 0.107 + 0.0152x \pm 0.028$ and for γA-myeloma $y = -0.002 + 0.589x \pm 0.0618$ Symbols as in fig 2

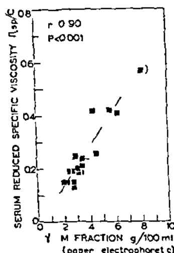

Fig 20 Relationship between paper electrophoretic γ+M-globulin and serum reduced specific viscosity in cases of marcoglobulinemia, with paper electrophoretic γ+M globulin up to 7.5 g/100 ml Regression eguation —0 016 + 0 0742x ± 0 0438

does not represent the effect of concentration alone but is a sum of several factors Hence the regression analyses in this evaluation of correlations between protein concentration and η_{sp} have been restricted in paper electrophoresis to concentrations up to 7 5 g 100 ml γ + M globulin. Moreover two cases of γA-myeloma (presented as white triangles) have been ruled out from the statistical analysis for the regression line of the respective group because the electrophoretic *mobility of paraproteins was of β-variety*

With these limitations the correlation between the serum reduced specific viscosity and the paper electrophoretic γ + M-fraction was statistically significant ($P < 0\ 01$) in the cases of γG myeloma while the same relationship for the cases of γA-myeloma, due to small number of cases left, was less convincing ($P < 0\ 05$) despite the good correlation coefficient ($r = 0\ 89$) (Fig 19) On the contrary, this relationship was stronger (Fig 20) in the γM paraproteinemia group Statistical analysis, in addition confirmed the visual impression that the coefficient of the regression line of the γG group differed significantly ($P < 0\ 001$) from those of the γA- and γM paraproteinemia groups but that the mutual difference between the γA and γM groups was not significant

Ultracentrifugal components with sedimentation constants 7 S and greater — In figs 21 22 and 23 serum relative viscosities are compared with the sum of proteins with sedimentation constants 7 S and greater in ultracentrifugal analyses i e with the sum of G-, Z- and M fractions in the respective groups For the reasons evident from fig 21 and already discussed in the preceding paragraph the statistical comparison of the data of these graphs were limited to protein concentrations up to 8 5 g/100 ml to avoid disturbance by the cases of γG paraproteinemia mentioned

In all the groups with paraproteinemia the correlations between the serum relative viscosity and the sum of major ultracentrifugal protein components were significant Moreover, it seemed that the more the molecular characteristics are known to deviate from those of the normal γ-globulins the better was the result of comparison

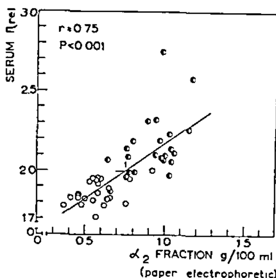

Fig 17 Relationship between paper electrophoretic α_2-globulin and serum relative viscosity in control and ankylosing spondylitis series Regression equation $y = 1.47 + 0.710x \pm 0.141$ Symbols as in fig 2

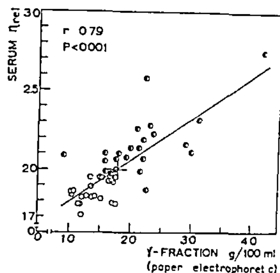

Fig 18 Relationship between paper electrophoretic γ-globulin and serum relative viscosity in control and ankylosing spondylitis series Regression equation $y = 1.54 + 0.264x \pm 0.133$ Symbols as in fig 2

tions has been used in the calculations throughout this study

If instead of the serum relative viscosity, the paper electrophoretic γ + M-fractions in the γG- and γA-myeloma groups and the macroglobulinemia series are plotted against the serum reduced specific viscosity, a better characterization between the various paraprotein properties and their amounts is obtained, as shown by figs 19 and 20 It is evident from fig 19 that, in principle, the correlation of the γG-paraprotein concentration to the serum reduced specific viscosity *would have been non-linear in this* material However, the departure from linearity evidently is caused by changes in the physicochemical milieu in the solution due to the increased molecular density because of the elevated total protein *concentration* Thus, the departing part of the curve

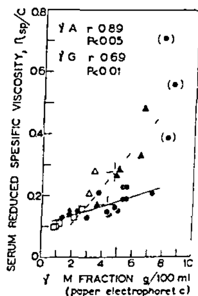

Fig 19 Relationship between paper electrophoretic γ + M-globulin and serum reduced specific viscosity in cases of γG- and γA-myeloma The values exceeding the electrophoretic protein concentration of 7.5 g 100 ml and the two cases of γA-myeloma (shown as white triangles) have been excluded for the reasons discussed in the text from the regression analyses The same is true for the cases of γμ-myeloma *Regression equation for* γG-myeloma $y = 0.107 + 0.0152x \pm 0.028$ and for γA-myeloma $y = -0.002 + 0.589x \pm 0.0618$ Symbols as in fig 2

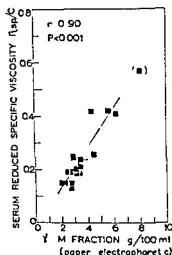

Fig 20 Relationship between paper electrophoretic , + M-globulin and serum reduced specific viscosity in cases of marcoglobulinemia, with paper electrophoretic , + M-globulin up to 7.5 g/100 ml Regression equation — 0 016 + 0 0742x ± 0 0438

does not represent the effect of concentration alone but is a sum of several factors Hence the regression analyses in this evaluation of correlations between protein concentration and η_{sp}/ have been restricted in paper electrophoresis to concentrations up to 7 5 g 100 ml , + M globulin Moreover two cases of ,A-myeloma (presented as white triangles) have been ruled out from the statistical analysis for the regression line of the respective group because the electrophoretic mobility of paraproteins was of β variety

With these limitations the correlation between the serum reduced specific viscosity and the paper electrophoretic , + M fraction was statistically significant ($P < 0 01$) in the cases of ,G myeloma while the same relationship for the cases of ,A-myeloma, due to small number of cases left, was less convincing ($P < 0 05$) despite the good correlation coefficient ($r = 0 89$) (Fig 19) On the contrary, this relationship was stronger (Fig 20) in the ,M paraproteinemia group Statistical analysis, in addition, confirmed the visual impression that the coefficient of the regression line of the ,G group differed significantly ($P < 0 001$) from those of the ,A- and ,M paraproteinemia groups but that the mutual difference between the ,A and ,M groups was not significant

Ultracentrifugal components with sedimentation constants 7 S and greater — In figs 21 22 and 23 serum relative viscosities are compared with the sum of proteins with sedimentation constants 7 S and greater in ultracentrifugal analyses i e with the sum of G-, Z- and M fractions in the respective groups For the reasons evident from fig 21 and already discussed in the preceding paragraph the statistical comparison of the data of these graphs were limited to protein concentrations up to 8 5 g 100 ml to avoid disturbance by the cases of ,G paraproteinemia mentioned

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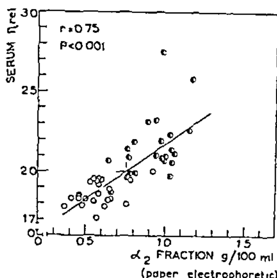

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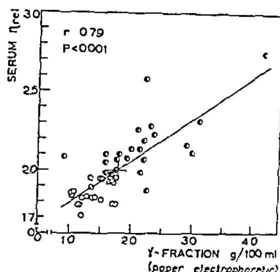

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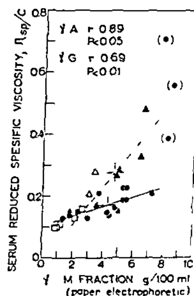

Fig 19 Relationship between paper electrophoretic γ + M-globulin and serum reduced specific viscosity in cases of γG- and γA-myeloma The values exceeding the electrophoretic protein concentration of 7.5 g 100 ml and the two cases of γA-myeloma (shown as white triangles) have been excluded for the reasons *discussed in the* text from the regression analyses The same is true for the cases of μ-myeloma Regression equation for γG-myeloma $y = 0.107 + 0.0152x \pm 0.028$ and for γA-myeloma $y = -0.002 + 0.589x \pm 0.0618$ *Symbols as in fig 2*

DISCUSSION

REPRESENTATIVITY OF PLASMA PROTEIN PATTERNS OF THE MATERIAL

The results of plasma and serum viscosity determinations gave surprisingly good correlations with the results of common laboratory methods of plasma protein study Before any general conclusions are to be drawn from the results of the study the representativity of the hematological data and plasma protein changes in the patient and control series has to be evaluated

A comparison of the results in the present control series to e g protein values of respective recent materials of *Wuhrmann & Marki* (1963) and of Sunderman (1964) in which the serum total protein concentration and the paper electrophoretic distribution of serum proteins were determined by comparable methods (by biuret methods and according to Grassmann & Hannig principle) revealed a good agreement The mean total protein and albumin concentrations of the control series in the present study were slightly higher than in the materials mentioned whereas other fractions were between the values or below the means of the materials in question

As to the protein data in the patient series Julkunen (1962), for instance, found in an extensive study of ankylosing spondylitis a mean serum total protein value of 8 19 g/100 ml for 115 males while the respective mean in this study was 8 28 g/100 ml for all the 22 patients with spondylitis The paper electrophoretic distribution of serum proteins also was very similar

In Sunderman s extensive survey the mean total protein content in a series of 67 patients with multiple myeloma was 7 96 g/100 ml of which the globulins comprised 5 35 g 100 ml (67 per cent) The respective serum total protein value in this study was exactly one gram higher with a concomitant higher mean of the globulin compartment in the paper electrophoresis 5 91 g/100 ml, which expressed in percentage gives, however, about the same figure (66 per cent) Likewise the mean serum total concentration of the present macroglobulinemia series was exactly one gram greater than in the material of *Sunderman* but the paper electrophoretic concentrations of paraproteins were of

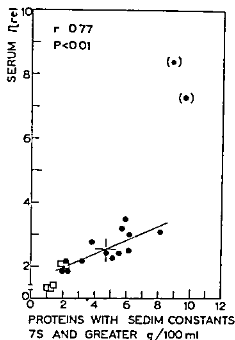

Fig 21 Relationship between proteins with sedimentation constants 7 S and greater and serum relative viscosity in cases of γG-myeloma The same relationship for γμ-myeloma is also shown, although these cases have not been taken in consideration in regression analysis Regression equation for γG-myeloma up to protein concentration of 8.5 g/100 ml $y = 1.54 + 0.213x \pm 0.342$

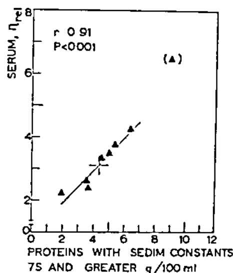

Fig 22 Relationship between proteins with sedimentation constants 7 S and greater and serum relative viscosity in cases of A-myeloma up to protein concentration of 8.5 g/100 ml Regression equation $y = 0.933 + 0.509x \pm 0.248$

The correlation of the ultracentrifugal M-fraction alone with the serum relative viscosity in patients with *macroglobulinemia was significant* ($r = 0.64$, $P < 0.01$), though less distinct than that of the sum of all the fractions excluding X- and A-fractions

The directions of the regression lines in figs 21, 22 and 23 differed significantly ($P < 0.001$) from each other There also was a significant difference between the γA and γM group regression lines although in paper electrophoretic analysis it was not significant

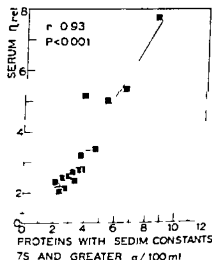

Fig 23 Relationship between proteins with sedimentation constants 7 S and greater in cases of macroglobulinemia up to protein concentration of 8.5 g/100 ml Regression equation $y = 0.058 + 0.862x \pm 0.368$

laboratory test, it may have been an acceptable solution to apply a simple capillary method despite its obvious rheological disadvantages Furthermore at the time of beginning of the study it also was the only possibility

An enhanced red cell aggregation has been noted in numerous diseases both *in vitro* and intravascularly but usually it per se and in its consequences is most marked in patients with profound plasma protein changes as in myeloma (Knisely *et al* 1947, Wasastjerna *et al* 1954 Marmont *et al* 1957, Larcan & Genetet 1964 Wells 1964), Waldenstrom's macroglobulinemia (Harders 1957, Schwab *et al* 1960, Wells 1964) and, e g , rheumatoid arthritis (Laine & Zilliacus 1950) The phenomenon was evident also in this study and caused some methodical problems in the determination of blood viscosity During the time the blood samples were heated to 37°C incipient aggregation was often noted Although the samples were moved during heating the aggregation became after some actual measurements of flow times so powerful that red cell aggregates began to settle to the bottom of the side tubes and capillary of the viscometer and a layer consisting mostly of plasma moved through the capillary Thus the red cell aggregation did not cause difficulties in the form of plugging of the capillary as would have been anticipated on the basis of findings *in vivo* but rather its effect was seen in a shortening of the flow times The same paradox was also observed by Ayrivie (1963) who also used a horizontal capillary tube Thereforsis of most regularly in cases of myel[illegible]va and macroglobulinemia the blooe-sample in the viscometer had to bef mixed well once more and new flow times were recorded for the sample In the control samples no macroscopic aggregation was noted Hence, no such mixing of sample was performed It is possible, however, that in control samples there was slight sedimentation which thus influenced the results The above is the most plausible explanation for the seemingly better accuracy of the viscosity determinations of whole blood in the myeloma series than in the controls

Due to the »disturbing» effect of sludging of red cell aggregates, the results for whole blood viscosity in this study and perhaps in other similar ones, must be considered less reliable than those for plasma and serum viscosities A powerful aggregation and settling of aggregates necessitates in all kinds of viscometers whether capillary or rotational some special arrangements

The effect of protein alterations on blood viscosity became evident also in correlation trials between whole blood viscosity and hematological parameters While in the control series significant correlations of comparable magnitude were obtained between whole blood viscosity and hemoglobin and hematocrit values the respective relationships in the dys- and paraproteinemia series were less distinct or insignificant The influence of high plasma viscosity, however, could be eliminated in the latter series (Fig

comparable magnitude, 41 5 and 45 per cent, respectively

It thus seems that at least in regard to plasma protein patterns the dys- and paraproteinemic patients as well as the control subjects of this study can well be considered representative of the diseases studied

COMMENTS ON THE VISCOMETRIC METHOD

The use of a new modification of a capillary viscometer in the present study and especially its effects on the viscosity values of blood, plasma and serum deserve some comment, because samples with a non-Newtonian behavioral pattern were tested The finding that the majority of blood viscosity values in cases with paraproteinemia were of the same order as the blood viscosity in cases of spondylitis and in the control series may at first seem surprising, since especially in Waldenstrom's macroglobulinemia the viscosity of blood generally has been thought to be very high on the basis of the clinical manifestations of the disease (e g, Gellhorn 1963) In an evaluation of the viscosity values it should be noted that the rather high velocity gradients used may, in addition to the low hematocrit values, explain the »low» levels in cases with paraproteinemia Therefore, in view of the behavior of viscosity of a non-Newtonian material like whole blood, it seems likely that had the viscosities of the samples been determined by recently developed low-shear methods, considerably higher values would have been obtained However, representative viscosity data obtained with these new methods have been published actually by few rheologists only, as could be seen from the review of the literature Low-shear rheology is, at present, in a phase of active progress, which manifests itself in several methodological reports, and no one evidently can tell which is the method of choice (Wayland 1965 b) in blood viscosity measurements Moreover, low-shear viscometric techniques give information, for example in the case of blood, on the degree of red cell aggregation and its effect on blood viscosity, and in the case of protein mixtures, on the influence of the shape and size of and aggregation phenomena between solvent molecules rather than on the effect of concentration on the viscosity of solutions High-shear methods, such as the conventional capillary viscometers, on the other hand, generally measure the effect of concentration (volume) of the suspended particles rather than that of other properties on the viscosity Accordingly, in this kind of correlative viscosity study in which the approach to the problem somewhat differs from those in pure rheological studies and which treats the determination of viscosity more as a

are not taken in consideration Correlations of the response of the viscosity to rising protein concentrations also showed significant qualitative differences between these groups These observations are well explainable on the basis of differences in the molecular characteristics of these two paraproteins of multiple myeloma

Bence Jones proteinemia or micromolecular paraproteinemia is a comparatively rare variant of multiple myeloma to which the recent papers of Solomon and Fahey (1964) and of Scheurlen (1965 a b) have attracted attention Although there were only five patients representing this type the results of their viscosity and protein analyses formed a homogeneous group, typical of which were the lowest values in regard to nearly every principal protein parameter Due to almost complete lack of earlier viscosity data in μ myelomas the author tried to peruse the literature on the viscosity values in cases of myeloma in the hope of finding similar cases which retrospectively could be regarded as micromolecular paraproteinemia Table 2 (p 24) reveals that case II published by Stewart & Weber (1938) had an erythrocyte sedimentation rate of 17 mm/h and a total protein value of 5 3 g 100 ml and Bence Jones protein was present in the urine — all features well fitting the clinical picture of Bence Jones proteinemia (Solomon & Fahey 1964 Scheurlen 1965 a b) and comparable with the respective values of the present series Furthermore, the low normal viscosities of serum and whole blood strongly support a retrospective diagnosis of micromolecular paraproteinemia Riva (1960) in his monograph, when presenting viscosity data in cases of myeloma (Table 2), wonders at the strikingly low serum relative viscosity value of 1 85 and the normal erythrocyte sedimentation rate in a case of myeloma despite the hyperproteinemic total protein value of 9 7 g/100 ml In later ultracentrifugal studies the paraprotein in the serum was found to have a low molecular weight of 83 000 and to be immunologically identical with Bence Jones protein in the urine Unfortunately no additional clinical data were given for a case with the lowest serum viscosity value of 1 57 and a serum total protein content of 6 5 g/100 ml among the four cases of myeloma presented by Jahnke *et al* (1958) Also the second case in the cryoglobulinemia series of Podivinsky *et al* (1962) with low values of serum viscosity and total protein content (Table 2) may have been a micromolecular paraproteinemia with cryoglobulinemia, because the patient had signs of renal insufficiency and traces of Bence Jones protein in the urine and because the only serum paper electrophoretic abnormality was α_2-hyperglobulinemia However, on the basis of these observations from the literature the only immunologically confirmed case of Bence Jones proteinemia in which viscosity studies were undertaken prior the present ones appears to be that of Riva (1960)

In view of the known physicochemical characteristics and the nearly spherical shape of the Bence Jones

comp… …ot in the spon- cent… …of the ratio to…

…the effect …tein concentra- …turbed the analyses …the plasma fibrinogen …ion The chemically esti- …fibrinogen concentration was …nd to correlate well with the difference in the viscosities of plasma and serum samples with the exception of plasmas from patients with paraproteinemia Petersen, who in 1953 introduced the viscometric determination of fibrinogen, made the same observation in some cases of myeloma, for which the viscometric method gave fictitiously high values In the present study, however, duplicate chemical determinations of fibrinogen in cases of myeloma and macroglobulinemia often showed some scatter This was thought to be due to inclusion of abnormal serum proteins in the fibrin clots, and according to Jacobsson (1955) such serum protein cannot be washed out The correlation coefficient between the two methods in the control and the ankylosing spondylitis series was exactly the same as that noted by Petersen for his control series (0 88) Also in these groups, the differences between duplicate fibrinogen values were considerably smaller Therefore, in the author's opinion the lack of correlation in paraproteinemia series between these two methods of fibrinogen determination might be due to errors in chemical estimation rather than in viscometric measurement of fibrinogen Since fibrinogen is known to be the most labile component of the plasma proteins (Luscher 1961), possibilities for errors in the viscometric determination increase in concentrated samples of high viscosity because of protein interactions, e g aggregation, and such physicochemical changes, thus, may be falsely interpreted to be caused by methodical factors

RELATION OF PROTEIN PROPERTIES TO VISCOSITY FINDINGS IN PARAPROTEINEMIA

In viscosity studies thus far reported in cases of multiple myeloma no particular attention was paid to possible differences in the viscosity of samples containing different paraproteins This aspect was one of the objects of the present study

The results showed that between γG- and γA-myeloma no clearcut differences could be observed in the relative viscosities of blood, plasma and serum if judged on the basis of mere relative viscosities However, a trend to display perhaps slightly higher serum viscosities was noted in the latter type of myeloma, best seen in the values of reduced specific viscosity when compared with the respective data in the γG group, especially if the three extreme cases in this group

ment of clinical symptoms (Fahey 1963, Fahey *et al* 1965, Smith *et al* 1965), particularly if the initial viscosity has been high Furthermore, the significantly diverging directions of the regression lines in figs 21, 22 and 23 make it possible to deduce that pathological proteins other than γG paraprotein are responsible for this divergence

TEMPERATURE DEPENDENCE OF VISCOSITY IN PARAPROTEINEMIC SERA

No marked differences in the temperature behavior of serum viscosities were observed between the samples from the various groups of multiple myeloma and from the macroglobulinemia series, with the exception of those from the γμ myeloma group which behaved like control and spondylitis sera Obviously the phenomenon of abnormal temperature response of viscosity is regulated for the greater part as fig 8 shows, by concentration dependent physicochemical laws (Jahnke et al 1958 Dintenfass 1965 a) Accordingly, the γG and γA paraprotein molecules in samples with elevated protein concentrations and concomitant high viscosities may on cooling form aggregates of macroglobulin-like molecules, and this may explain the similarities of the temperature dependence of viscosity above a critical viscosity value It is therefore, evident that the usefulness of indexes such as TVI is somewhat limited as has been noted by Waldenstrom (1952) and Jahnke *et al* (1958) and others This does not mean that thermoviscometry *per se* would not be useful On the contrary, it offers in the diagnosis of cryoglobulinemias, for instance a more rapid method than those in common use at present, even though the quantitative estimation of cryoglobulins does not appear possible at present.

POSSIBILITIES FOR THE CLINICAL APPLICATION OF VISCOMETRY

Although the determination of serum or plasma viscosity by an *in vitro* capillary procedure does not give information on the microcirculatory status *in vivo* as pointed out by e g Fahey *et al* (1965) and although the results rarely are compatible with those of whole blood viscosity measurements even under *in vitro* circumstances their use as a correlative screening test is indicated in several instances for the following *reasons*

The determination of serum or plasma viscosity must be regarded as a non specific test such as the erythrocyte sedimentation rate, SIA or certain other lability tests However, the good correlations with the results of

protein molecule (Putnam 1960), the low serum viscosity and the slight effect of increasing concentration on it are conceivable If further observations on viscosity in this relatively rare variety of myeloma also reveal low or normal values of serum viscosity, the latter could be readily employed as a useful adjunct and screening test in the diagnosis of the condition

Waldenstrom's macroglobulinemia has generally been regarded as a state in which the viscosity of serum, plasma and whole blood is higher than in other diseases characterized by profound plasma protein changes The literature reviewed and the results of the present study indicate, however, that in multiple myeloma, for instance, high serum and plasma viscosity values and the consequent clinical symptoms such as microcirculatory impairment with retinopathy, bleeding diathesis, cardiac failure and neurological symptoms are not extreme rarities Likewise in cases of macroglobulinemia, serum viscosities just exceeding the upper limits of the normal range may occur if the relative macroglobulin concentration is below 20 per cent of the proteins When cases with the latter benign, often asymptomatic, variety of primary macroglobulinemia are diagnosed more frequently, the classical laboratory picture in respect to the viscosity findings may need some reconsideration

Increased paraprotein levels alone in multiple myeloma, on the other hand, were insufficient to explain the disproportionally high viscosity values observed in three cases of γG myeloma (Cases 1, 2 and 3) Evidently there must be an environmental physicochemical change at the molecular level, for instance, in the form of aggregation to larger »macromolecules» Although this possibility of protein — protein interaction was not specifically corroborated by experimental studies, as in the two cases of Smith *et al* (1965), it remains the most plausible explanation for high serum viscosities greatly diverging from those expected on basis of the protein concentrations Obviously also this kind of extreme viscosity values in myeloma invalidate the use of the method suggested by Ratcliff *et al* (1963) for the viscometric distinction between macroglobulinemia and myeloma, since at least in the present series no difference could be noted between the values in these two diseases

While in γG-myeloma high viscosity values were the exception rather than the rule, in macroglobulinemia and also in γA-myeloma the steep rise of viscosity in relation to the moderate elevation in the protein concentration as well as the remarkably good correlation of serum viscosity with the paraprotein concentrations are compatible with the fact that these states, particularly macroglobulinemia, are especially predisposed to the hyperviscosity syndrome It is just the steepness and non-linearity of the viscosity (para)protein curve which explains that small reductions of paraprotein concentrations by plasmapheresis may effect a considerable drop in viscosity with concomitant abate-

ment of clinical symptoms (Fahey 1963, Fahey et al 1965, Smith et al 1965), particularly if the initial viscosity has been high Furthermore the significantly diverging directions of the regression lines in figs 21, 22 and 23 make it possible to deduce that pathological proteins other than γG-paraprotein are responsible for this divergence

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The determination of serum or plasma viscosity must be regarded as a non specific test such as the erythrocyte sedimentation rate, SIA, or certain other lability tests However the good correlations with the results of

clinical methods of protein study as well as with qualities and concentrations of pathological proteins show a better sensitivity and obvious advantages of this determination over screening tests used in the diagnosis and characterization of dys- and paraproteinemia Of the advantages over the determination of the erythrocyte sedimentation rate, recently summarized by e g Harkness (1963) and Eastham & Morgan (1965), may be mentioned that serum or plasma viscosity

— shows narrow normal ranges for both sexes and for all ages except possibly for persons of very advanced age,

— is not affected by red cell factors (anemia and polycythemia),

— elevations are closely related to the clinical severity of the disease, because viscosity measures practically only the increments of proteins with non-globular shape Therefore, viscosity measurement rapidly reveals whether a high erythrocyte sedimentation rate is caused by elevated plasma fibrinogen or by increases in serum proteins, e g by paraproteins

The diagnostic unreliability of the SIA test has been noted, in addition to the present study, in several instances (Mackay *et al* 1956, Steel 1959 b, Laurell & Waldenstrom, 1961) The advantages of serum viscosity determination in comparison to this widely used screening test for macroglobulinemia are obvious

As appears from the literature, serum viscometry can be used as a valuable adjunct in the diagnosis of typical cases of macroglobulinemia, especially when advantage is taken of the special characteristics of these proteins In addition, the diagnostic aid of viscometry in the distinction of $\gamma\mu$-paraproteinemia from other types of myeloma seems possible A simple, cheap and rapid combined study of plasma and serum viscosities before, e g, serum ultracentrifugal analysis and immunoelectrophoresis would also facilitate the selection of samples for this type of costly and time-consuming analyses, which in smaller centers are often overloaded because of their indiscriminate use Even if the diagnosis of macroglobulinemia is made by the latter analyses, the simultaneous serum viscosity value serves as a valuable reference, since, as Fahey (1963) has stressed, »in actual practice the serum viscosity measurement and clinical observation are the two most important parameters in following the patient with macroglobulinemia and hyperviscosity symptomatology» The effectiveness of plasmapheresis therapy in these patients offers the best evidence of the good correlation between high serum viscosity and circulatory disturbances as illustrative examples in the papers of Fahey and co-workers show

One of the practical points which result from the use of serum samples instead of whole blood in viscosity determination is, in addition to the fewer factors affecting the result, the possibility of transportation and freezing of the samples Viscometry at various temperatures quickly gives a clue

to the possible presence of cryoproteins in a sample Furthermore, in appropriate cases viscometry can be used also for the rapid estimation of the plasma fibrinogen concentration

In cases suspected to present paraprotein aggregation which may otherwise be demonstrable only by very elaborate and difficult physicochemical protein studies, viscometry can be used as one of the methods (Smith et al 1965, Vaerman et al 1965) as well as for the physicochemical characterization of isolated paraproteins

The possibilities offered by clinical viscometry are probably of the greatest aid when used in conjuction with *in vivo* and *in vitro* procedures aimed at the determination of degree of aggregation of red cells The combined application of these methods, for instance according to the principles outlined by Wells (1964), may be helpful *in the evaluation of dys- and* paraproteinemic patients with microcirculatory disturbances and in the planning and observation of their rational therapy

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— elevations are closely related to the clinical severity of the disease, because viscosity measures practically only the increments of proteins with non-globular shape. Therefore, viscosity measurement rapidly reveals whether a high erythrocyte sedimentation rate is caused by elevated plasma fibrinogen or by increases in serum proteins, e.g. by paraproteins.

The diagnostic unreliability of the SIA test has been noted, in addition to the present study, in several instances (Mackay *et al.* 1956, Steel 1959 b, Laurell & Waldenstrom, 1961). The advantages of serum viscosity determination in comparison to this widely used screening test for macroglobulinemia are obvious.

As appears from the literature, serum viscometry can be used as a valuable adjunct in the diagnosis of typical cases of macroglobulinemia, especially when advantage is taken of the special characteristics of these proteins. In addition, the diagnostic aid of viscometry in the distinction of $\gamma\mu$-paraproteinemia from other types of myeloma seems possible. A simple, cheap and rapid combined study of plasma and serum viscosities before, e.g., serum ultracentrifugal analysis and immunoelectrophoresis would also facilitate the selection of samples for this type of costly and time-consuming analyses, which in smaller centers are often overloaded because of their indiscriminate use. Even if the diagnosis of macroglobulinemia is made by the latter analyses, the simultaneous serum viscosity value serves as a valuable reference, since, as Fahey (1963) has stressed, »in actual practice the serum viscosity measurement and clinical observation are the two most important parameters in following the patient with macroglobulinemia and hyperviscosity symptomatology». The effectiveness of plasmapheresis therapy in these patients offers the best evidence of the good correlation between high serum viscosity and circulatory disturbances as illustrative examples in the papers of Fahey and co-workers show.

One of the practical points which result from the use of serum samples instead of whole blood in viscosity determination is, in addition to the fewer factors affecting the result, the possibility of transportation and freezing of the samples. Viscometry at various temperatures quickly gives a clue

to the possible presence of cryoproteins in a sample Furthermore, in appropriate cases viscometry can be used also for the rapid estimation of the plasma fibrinogen concentration

In cases suspected to present paraprotein aggregation, which may otherwise be demonstrable only by very elaborate and difficult physicochemical protein studies, viscometry can be used as one of the methods (Smith et al 1965 Vaerman et al 1965) as well as for the physicochemical characterization of isolated paraproteins

The possibilities offered by clinical viscometry are probably of the greatest aid when used in conjuction with *in vivo* and *in vitro* procedures aimed at the determination of degree of aggregation of red cells The combined application of these methods, for instance according to the principles outlined by Wells (1964), may be helpful in the evaluation of dys- and paraproteinemic patients with microcirculatory disturbances and in the planning and observation of their rational therapy

SUMMARY

The purpose of the present study was to measure the relative viscosities of blood, plasma and serum in patients with dys- an paraproteinemia The temperature-dependent changes in viscosity between samples from different series and individuals with plasma protein disorders were also compared in order to find out the usefulness of thermoviscometry The viscosity data were correlated with some hematological parameters and with the plasma protein patterns as examined by determinations of the serum total protein and plasma fibrinogen concentrations and by paper electrophoretic, immunoelectrophoretic and ultracentrifugal analyses of the serum The aim of these comparisons was to assess the applicability of capillary viscometry as a laboratory tool and to obtain information on whether a viscometric characterization and differentiation of various paraproteinemias from each other is possible

The blood samples were obtained from 30 patients with multiple myeloma, 17 patients with macroglobulinemia, 22 patients with ankylosing spondylitis and 24 healthy control persons of various ages

The viscosities (*relative to water*) were determined at three temperatures by two horizontal glass capillary viscometers in which the flow of the samples was produced by using positive pressures as the *driving head*

The main results obtained were as follows

Blood viscosity — Apart from some high values of blood viscosity in the multiple myeloma and macroglobulinemia series, the majority of the values of relative viscosity of whole blood in these series were within the ranges of the control and the spondylitis series Neither did the medians of the patient series differ clearly from that of the controls However, the five cases of ,u-myeloma showed the lowest viscosities among the paraproteinemias

Plasma viscosity — The medians and ranges of plasma relative vicosity in the myeloma and the macroglobulinemia series reached much higher levels and were markedly wider than those in the ankylosing spondylitis and control series The control series had a distinctly lower median value with a narrower range of plasma viscosity than the spondylitis patients The mean

value of the plasma viscosity in the controls was of the same order as that in the $\gamma\mu$ myeloma group which showed the lowest values among the different categories of the paraprotein emia series

Serum viscosity — The serum viscosity data were, in principle, similar to the plasma viscosity findings Al though the myeloma and the macroglobulinemia series, when compared with the spondylitis and the control series showed markedly higher median levels and wider ranges of serum relative and reduced specific viscosities, which were further accentuated by some extreme values these paraproteinemia series did not mutually differ distinctly Among the paraproteinemias, the cases of micromolecular myeloma exhibited again clearly the lowest values of serum viscosity, comparable to the values in the control series

Temperature dependence of viscosity — In principle the increments of the viscosity with falling temperature were with comprehensible devia tions analogous for blood plasma and serum samples The similarity of the behavior of viscosity in the various paraproteinemia sera (with the exception of $\gamma\mu$ myeloma sera) as well as the fact that the temperature response of the viscosity obviously is regulated by concentration dependent physicochemical laws invalidate the use of thermoviscometry in the distinction of various blood protein disorders from each other except for the cases with cryoglobulinemia

Correlations of viscosity to hematological and plasma protein data — Hemoglobin and hematocrit values showed significant correlations with the relative viscosity of blood *only in* the control series, whereas in the dys- and paraproteinemic series less distinct or insignificant relationships were obtained The use of the ratio Blood η_{rel}/ Plasma η_{rel} instead of mere whole blood viscosity, however, eliminated the disturbing effect of high plasma viscosity, making the correlation to hematocrit statistically significant in cases of paraproteinemia

Plasma relative viscosity correlated significantly to the one-hour erythrocyte sedimentation rate in the control and ankylosing spondylitis series but no correlation seemed to exist in patients with paraproteinemia

Likewise, a significant relationship was observed between the specific viscosity of fibrinogen (difference between plasma and serum viscosities) and chemically determined plasma fibrinogen in the control and spondylitis series The same relationship, although significant was clearly less convincing in cases of myeloma and macroglobulinemia

Significant correlation were noted between the serum total protein concentration and the serum relative viscosity in all series In cases of para proteinemia the non linearity of this relationship usually the more apparent the higher the concentration of abnormal proteins was and the more the molecular properties of the para proteins are known to deviate from those of the normal γ-globulins

SUMMARY

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Comparisons of the serum relative viscosity with the paper electrophoretic α_2- and $\gamma(+M)$-fractions gave significant correlations in the control, the spondylitis and the paraproteinemia series However, when the paper electrophoretic paraprotein concentrations in the γG- and γA-myeloma groups and in the macroglobulinemia series were correlated to the serum reduced specific viscosity, a still better characterization of the viscometric behavior of these proteins was obtained In addition to the significant relationships between the paraprotein concentrations and serum reduced specific viscosities the regression lines of the γM and γA groups were significantly steeper than that of the γG group in relation to the increment of the paraprotein concentration

In the γG-, γA- and γM- paraproteinemia groups strong correlations were found between the serum relative viscosity and the sum of ultracentrifugal proteins with sedimentation constants 7 S and greater Moreover, the directions of the regression lines of the γG-, γA- and γM-paraproteinemia groups differed significantly from each other

Thus every paraprotein fraction studied seems to have its own characteristic effect on the viscosity, based on its molecular properties The results of the present study show that capillary viscomentry can provide useful information in the study of rheological properties of blood, plasma and serum samples from patients with plasma protein disorders when it is used in conjunction with other pertinent laboratory methods

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APPENDIX

TABLES OF INDIVIDUAL VALUES

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Table 8 MULTIPLE MYELOMA SERIES

Group I γG — myelomas

Case number and name	Age and sex	Hb g/100 ml	RBC x10⁶/cu mm	MCH μμg	Hct vol %	WBC /cu mm	ESR mm/h	Serum total protein concentration g/100 ml	Paper electrophoretic distribution: Albumin g/100 ml	Globulins α_1	α_2	g/100 ml β	γ+M
1 OV	52 M	8 8	2.50	34	.3 0	4 800	15[illegible]	10 5	1 39	0 [illegible]9	0 57	0 45	7 80
2 EL	45 F	9 4	3 72	.5	6 0	15 00	130	11 3	1 99	0 [illegible]0	0 15	0 50	8 46
3 UK	30 F	7 6	2 52	30	24 0	8 300	151	11 1	1 98	0 [illegible]0	0 24	0 46	8 22
4 AK	65 M	10 0	3 10	33	31 0	3 000	138	12 3	3 36	0 3[illegible]	0.55	0 8[illegible]	7 25
5 AK	58 M	11 0	4 12	.7	35 5	3 600	122	11 0	3 75	0 30	0 57	0 9[illegible]	5 56
6 HL	75 F	9 9	3 00	33	31 5	2 300	147	9 3	2 66	0 30	0 56	0 45	5 33
7 KH	60 M	11 2	2 79	40	35 0	3.300	112	10 8	4 03	0 .0	0 44	0 59	5 55
8 JK	56 M	9 8	3 17	31	31 5	9 200	137	10 5	3 14	0 38	0 74	0 49	5 45
9 VS	67 M	6 0	1 66	34	[illegible]0 0	1 00	160	8 6	2 88	0.35	0 87	0 86	3 70
10 AL	75 F	10 4	3 [illegible]8	32	4 0	3 300	106	9 1	2 50	0 50	0 74	0 62	4 76
11 ES	52 F	8 5	3 00	[illegible]8	30 5	9 500	109	9 4	2 80	0 34	0 77	0.53	4 97
12 HK	60 F	13 6	4 08	33	44 0	5 400	77	9 4	2 94	0 38	0 91	0 85	4 32
13 JT	73 M	9 8	3 00	33	36 0	9 400	24	8 9	3 05	0 40	0 60	0 49	4 44
14 MA	40 M	11 8	4 15	8	41 5	8 500	83	8 8	4 08	0 34	0.52	0 87	2 98
15 TR	63 M	13 9	3 50	39	38 0	4 400	91	7 7	3 70	0.30	0 70	0 66	2 35
16 JK	70 F	13 0	4 50	29	43 5	3 900	107	6 0	2 26	0 44	0 85	0 65	1 80
17 JT	60 M	12 0	4 31	28	43 0	2 800	74	6 3	2 96	0 25	0 96	0 73	1 40

Table 8 continued

	Albumin globulin ratio	Plasma fibrinogen concentration mg/100 ml	Immunoelectrophoresis Main immunoglobulin	Fractions in serum ultracentrifugal analysis g/100 ml: X	A	G	Z	M	SIA test	Presence of cryo glob	Presence of cryo fibrinog	Urine B J protein
1	0 15	3[illegible]0	γG	0 1	1 6	8 8	—	—	+++	+	—	—
2	0 21	[illegible]06	γG	0 [illegible]	1 5	9 6	—	—	—	—	—	—
3	0	194	γG						—	—	—	—
4	0 37	511	γG						+	—	—	—
5	0 49	364	γG	0 7	4 4	5 9	—	—	+	—	—	—
6	0 40		γG	0 3	3 3	5 6	—	0 1	—	—	—	—
7	0 63	4 0	γG	0 7	[illegible]0	7 8	—	0 3	—	—	—	—
8	0 43	550	γG	0 5	3 8	6 1	—	0 1	—	—	—	+
9	0 50	43[illegible]	γG	1 0	3 8	3 8	—	—	—	—	—	+
10	0 34	[illegible]89	γG	0 4	2 6	5 8	—	0 3	—	—	—	—
11	0 4[illegible]	439	γG	0 3	3 4	5 3	—	0 2	—	—	—	+
12	0 46	504	γG	0 9	3 8	4 3	—	0 4	—	—	—	—
13	0 51	170	γG	0 4	3 4	5 0	—	0 1	—	—	—	—
14	0 86	634	γG	0 9	4 7	2 9	—	0 3	—	—	—	—
15	0 93	490	γG	0 4	5 1	2 1	—	0 1	+	—	—	—
16	0 59	270	γG	0 8	3.2	1 9	—	0 1	—	—	—	—
17	0 88	5 7	γG	0 5	3 5	[illegible]1	—	0 2	—	—	—	—

ABBREVATIONS USED IN THE TABLES OF APPENDIX

Hb = hemoglobin concentration RBC = red blood cell count MCH = mean corpuscular hemoglobin Hct = hematocrit value WBC = white blood cell count ESR = erythrocyte sedimentation rate B J = Bence Jones TVI = temperature — viscosity index

9	4 65	4 65	4 57	4 53	3 78	3 79	3 87	3 77	3 47	3 42	3 35	3 38
10	2 79	2 80	2 8^	2 89	2 82	2 79	2 77	2 71	84	2 80	2 68	2 70
11	3 45	3 ^9	3 12	3 13	3 08	3 02	3 06	2 98	2 74	2 67	2 70	2 70
12	3 40	3 8	3 _3	3 15	3 13	3 08	3 13	3 09	3 24	3 17	3 00	2 94
13	2 60	2 60	2 42	2 40	2 52	2 46	44	2.38	^ 50	2 42	2 40	2 43
14	3 10	2 96	2 94	2 89	2 85	2 87	2 78	2 74	3 10	2 75	^ 68	2 67
15	2 80	2 70	^ 73	2 71	2 79	2 72	2 73	2 70	2 67	_ 66	2 54	2 6
16	2 70	2 59	2 46	2 46	2 35	2 43	2 36	2 _2	2 43	2 42	2 42	2 40
17	2 14	2 11	2 22	2 17	2 09	2 10	2 13	2 14	2 3_	2 23	2 43	2 38

Table 8 continued SERUM RELATIVE VISCOSITY*)

	10 C				0 C				37 C				Serum reduced specific viscosity	TVI $\frac{\eta r\ 10\ C}{\eta r\ 37\ C} \times 100$
	O 0 65		O 0 51		O 0 65		O 0 51		O 0 65		O 0 51			
	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg		
1	9 ^0	9 5	24 15	^3 10	13 35	18 50	17 00	16 45	8 40	8 05	7 60	7.85	0 71	348
2	9 3	9 27	9 08	9 05	8 35	8 30	8 49	8 34	7 8	7 04	6 83	6 77	0 6	127
3	9 25	8 05	8 13	7 78	6 ^3	6 20	6 18	5 93	5 29	5 17	5 ^4	5 25	0 39	157
4	4.39	4 32	4 14	4 25	3 88	3 86	3 93	3 85	3 63	3 63	3 64	3 66	0 21	1^1
5	4 09	3 96	3 71	3 68	3 61	3 58	3 59	3 48	3 48	3 39	3 ^6	3 23	0 23	117
6	3 58	3 48	3 38	3 29	2 94	2 88	2 84	2 82	3 15	3 16	3 04	3 05	0 23	114
7	3 66	3 62	3 51	3 53	3 14	3 12	3 08	3 04	3 08	3 06	3 08	3 07	0 19	119
8	3 44	3 40	3 48	3 40	3 ^6	3 22	3 27	3 0	2 99	2 94	94	_ 95	0 19	115
9	3 08	98	3 00	2 96	2 85	2 79	2 76	2 71	2 76	2 70	2 67	2 67	0 ^1	111
10	2 64	^ 74	2 63	2 62	2 36	2 41	2 30	2 ^3	^ 48	^ 40	2 47	2 44	0 16	106
11	2 7	75	2 78		2 5^	2 52	2 54	2 32	2 42	2 42	2 33	^ 34	0 15	112
1^	2 71	2 63	2 65	2 63	2 44	2 48	57	2 48	2 41	2 38	2 32	2 31	0 15	11^
13	44	30	2 31	_ 32	2 13	2 11	2 09	2 07	2 24	2 _0	2 18	2 18	0 14	109
14	2 31	2 30	2 27	2 27	2 24	2 ^0	2 20	2 15	2 17	2 12	2 06	2 05	0 13	107
15	2 14	2 08	2 14	2 10	2 14	2 12	2 03	2 00	2 15	2 15	13	2 09	0 15	100
16	1 87	1 8^	1 82	1 78	1 83	1 79	1 70	1 76	1 86	1 83	1 82	1 8^	0 14	100
17	1 88	1 72	1 76	1 73	1 75	1 70	1 75	1 69	1 83	1 75	1 71	1 64	0 13	10^

*) measured at three temperatures (10 0 and 37 C) with two capillaries of 0 65 mm and 0 51 mm diameters with positive pressures of 100 mmHg and 50 mmHg

Table 8 *continued* BLOOD RELATIVE VISCOSITY*)

	10 C				20 C				37 C			
	Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51	
	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg
1	58 50		52 70		33 80	30 10	32 90	31 90	15 20	13 70	13 20	12 00
2	10 95		8 46		9 60	9 29	8 72	7 65	9 61	9 24	8 88	8 04
3	8 77		7 15		7 17	6 82	6 29	5 73	6 75	5 92	5 64	5 28
4	9 78		7 65		7 86	7 13	7 06	6 54	6 80	6 47	5 89	5 46
5	8 80		7 26		7 44	6 70	5 9[illegible]	5 42	6 91	6 33	5 88	5 46
6	7 47		7 00		3 81	3 81	3 67	3 58	4 08	3 66	3 32	3 07
7	6 59		5 31		6 83	5 93	5 26	3 82	5 46	5 13	4 67	4 37
8	7 69		5 83		6 03	5 83	5 14	4 78	5 33	5 26	5 08	4 59
9	5 97		5 47		5 21	4 93	4 84	4 33	4 97	4 30	3 80	3 75
10	4 62		4 03		4 59	4 91	4 61	4 34	4 33	4.32	3 50	3 43
11	4 75		4 03		4 72	4 53	4 54	3 81	5 30	5 14	4 92	4 51
12	8 84		8 50		7 49	7 20	6 97	5 93	6 77	6 79	6 65	6 15
13	5 48		4 57		6 33	6 [illegible]0	6 22	5 96	5 10	4 92	4 40	4 20
14	7 28		6 [illegible]0		5 77	5 75			5 64	5 49	5 30	4 70
15	6 42		5 82		5 74	5 82	5 27	5 00	5 36	5 28	5 01	4 85
16	6 66		4 87		5 17	5 05	5 19	5 46	4 46	4 32	4 64	4 18
17	5 27		5 68		5 52				4 86		3 09	

Table 8 continued PLASMA RELATIVE VISCOSITY*)

	10 C				20 C				37 C			
	Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51	
	100 mmHg	*50 mmHg*	*100 mmHg*	*50 mmHg*	*100 mmHg*	*50 mmHg*	*100 mmHg*	*50 mmHg*	*100 mmHg*	*50 mmHg*	*100 mmHg*	*50 mmHg*
1	30 90	29 30	21 35	21 45	13 45	13 15	16 55	16 10	8 25	8 07	7 54	7 57
2	10 25	9 93	10 30	10 15	8 15	8 41	8 39	8 67	8 66	8 11	7 94	7 92
3	10 80	10 [illegible]5	9 61	9 28	6 37	6 21	5 68	5 66	5 [illegible]6	5 53	5 65	5 65
4	5 78	5 70	5 62	5 26	4 66	4 72	4 82	4 88	4 28	4 23	4 08	4 02
5	5 10	5 04	4 7[illegible]	6 95	4 12	4 03	4 29	4 46	4 24	4 15	4 07	4 04
6	3 67	3 [illegible]5	3 [illegible]0	3 [illegible]0	3 14	3 12	3 01	2 94	3 29	3 23	3 12	3 11
7	3 96	4 01	3 68	3 83	3 54	3 58	3 [illegible]6	3 49	3 45	3 43	3 40	3 32
8	4 14		4 15	4 13	3 80	3 80	3 82	3 77	3 79	3 71	3 72	3 78

Table 9 continued BLOOD RELATIVE VISCOSITY)

	10 C				0 C				37 C			
	O 0 65		O 0 51		O 0 65		O 0.51		O 0 65		O 0 51	
	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg
18	11 90		10 82		9 10	8 40	7 54	7 03	7 71	5 78	5 94	5 49
19												
0	8 87		7 36		6 32		6 10		6 25		5 05	
21	7 73		6 70		5 96	4 96	5 94	4 86	5 82	5 12	4 65	4 43
2	11 75		10 02		8 65	8 50	7 85	6 78	6 48	6 1?	5 74	5 79
3	5 06		4 38		4 87	3 70	3 22		4 27	3 84	3 47	3 42
24	4.33		3 68		3 97	3 82	3 63	3 9	3 80	3 65	3 44	3 16
5	5 86		4 69		5 62	5.58	4 75	3 94	5 0	5 10	4 40	4 08
26	5 30		4 20		4 82	4 60	3 62	3 37	4 9	4 32	4 03	3 59
7	3.39		3 08		3 06	2 64	2 99	2 66	3 22	2 90	2 55	2 42
28	6 36		6.30		4 3	3 80	4 97	5 1	4 8	3 91	4 28	4 40
29	2 60		3 01		2 60	2 56	2 59	2 51	2 86		2 68	
30	3 43		3 6		3 03	98	2 96	2 79	3 15	3 0?	2 85	2 76

Table 9 continued PLASMA RELATIVE VISCOSITY*)

	10 C				0 C				37 C			
	O 0 65		O 0 51		O 0 65		O 0.51		O 0 65		O 0 51	
	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	0 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg
18	15 45	15 50	15 70	14 72	10 07	10 06	10 02	10 00	7 60	7 47	7 39	7 35
19	6 86	6 85	6 81	6 90	6 00	5 97	5 93	5 9?	5 .6	5 50	5 12	5 17
0	6 30	6 35	6 18	6 14	5 21	5 30	4 93	5 07	5 03	5 14	4 70	4 81
21	5 09	5 87	5 63		4 73	4 72	4 74	4 67	4 56	4 46	4 40	4 36
2	7 32	7 40	7 5	7 47	4 63	4 60	4 90	4 93	3 89	3 96	3 84	3 84
23	3 44	3 30	3 21	3 12	3 00	2 93	3 01	2 94	2 92	2 90	2 78	2 80
24	3 06	2 98	2 96	2 85	2 77	2 74	2 75	2 7?	2 69	2 65	2 69	2 69
5	3 ?2		3 10		2 74	2 63	2 69	2 71	2 62	2 57	2.54	2 50
6	2 92	2 69	2 70	2 62	2 52	2 52	? 65	2 51	2 47	2 44	2 38	2 36
27	2 35	2 3	2 33	2 8	2 17	2 17	2 18	2 15	2 43	2 36	2 37	2 37
28	2 39				2 32	2 6	2 36	2 6	2 69	2 67	2 68	2 64
?9	2 04	1 85	1 91	1 87	1 88	1 85	1 83	1 78	1 95	1 88	1 86	1 82
30	1 97	1 93	1 80	1 81	1 88	1 88	1 90	1 88	1 96	1 91	1 87	1 86

*) measured at three temperatures (10 20 and 37 C) with two capillaries of 0 65 mm and 0 51 mm diameters with positive pressures of 100 mmHg and 50 mmHg

Case number and name	Age and sex	Hb g/100 ml	RBC x10⁶/cu mm	MCH μμg	Hct vol %	WBC /cu mm	ESR mm/h	Serum total protein concentration g/100 ml	Paper electrophoretic distribution: Albumin g/100 ml	Globulins g/100 ml α_1-	α_2-	β-	γ+M
18 EH	60 F	8 0	2 38	34	24 5	1 600	150	11 5	2 46	0 31	0 55	1 54	6 65
19 FF	58 M	8 1	2 54	32	24 5	6 000	149	10 2	2 12	0 40		1 25	6 43
20 VL	48 M	9 9	3 20	31	29 5	6 300	132	9 9	3 33	0 28	0 57	0 70	5 02
21 EE	75 M	9 8	3 63	27	29 0	11 000	139	9 4	2 48	0 43	0 92	0 65	4 92
22 VJ	50 M	11 3	4 05	28	38 0	6 200	128	8 5	3 82	0 27	0 69	3 34	0.39
23 OL	73 F	9 3	3 80	25	32 0	5 600	134	7 7	3 27	0 30	0 64	3 06	0 43
24 AV	65 M	8 5	2 68	32	24 5	5 500	149	7 9	2 32	0 46	0 70	0 77	3 62
25 UK	67 M	11 2	3 50	32	40 5	6 100	119	8 2	4 34	0 46	0 78	0 73	1 89
Group III γμ-myelomas													
26 AL	52 F	12 6	3 90	32	36 5	6 000	86	8 1	3 48	0 53	1 10	0 87	2 12
27 IM	65 F	8 2	2 70	30	26 5	4 200	148	6 5	2.54	0 43	0 53	2 58	0 44
28 PP	59 M	13 6	4 34	32	39 0	7 200	30	7 2	4 61	0 40	0 61	0 71	0 87
29 VM	60 F	8 7	2 70	32	36 5	3 000	40	6 0	3 31	0 25	0 78	0 45	1 21
30 HP	60 F	6 9	2 20	32	24 0	7 800	76	6 6	3 93	0 37	0 79	0 70	0 91

Table 9 continued

	Albumin globulin ratio	Plasma fibrinogen concentration mg/100 ml	Immunoelectrophoresis Main immunoglobulin	Fractions in serum ultracentrifugal analysis g/100 ml: X	A	G	Z	M	SIA test	Presence of cryo-: glob	fibrinog	Urine B J protein
18	0 27	386	γA	—	2 5	6 9	1 85	0 25	—	—	—	—
19	0 26	488	γA	0 7	3 1	4 4	2 0	—	—	—	—	+
20	0 51	388	γA	0 6	3 9	2 8	2 6	—	—	—	—	—
21	0 36	548	γA	0 6	3 8	2 2	2 8	—	—	—	—	—
22	0 81	416	γA	0 2	3 8	3 6	0 5	0 4	—	+	—	—
23	0 73	434	γA	0 3	3 8	2 1	1 5	—	—	—	—	—
24	0 43	375	γA	0 9	3 3	3 7	—	—	—	—	—	—
25	1 15	395	γA	0 7	4 9	1 8	0 6	0 2	—	—	—	—
26	0 75	575										
27	0 63	355	γμ	0 9	5 3	1 7	—	0 2	±	—	—	++
28	1 83	557	γμ	0 6	3 7	1 8	0 2	0 2	—	—	—	++•
29	1 24	354	γμ	1 1	5 0	1 0	—	M₁ 0 3, M₂ 0 1	—	—	—	—
30	1 38	478	γμ	0 7	4 0	1 1	—	0 2	—	—	—	+

Table 9 continued BLOOD RELATIVE VISCOSITY*)

	10 C Ø 0 65 100 mmHg	10 C Ø 0 65 50 mmHg	10 C Ø 0 51 100 mmHg	10 C Ø 0 51 50 mmHg	0 C Ø 0 65 100 mmHg	0 C Ø 0 65 50 mmHg	0 C Ø 0 51 100 mmHg	0 C Ø 0 51 50 mmHg	37 C Ø 0 65 100 mmHg	37 C Ø 0 65 50 mmHg	37 C Ø 0 51 100 mmHg	37 C Ø 0 51 50 mmHg
18	11 90		10 82		9 10	8 40	7 54	7 03	7 21	5 8	5 94	5 49
19												
20	8 87		7 36		6 32		6 10		6 25		5 05	
21	7 73		6 70		5 96	4 96	5 94	4 86	5 82	5 12	4 65	4 43
22	11 75		10 07		8 65	8 50	7 85	6 78	6 48	6 12	5 74	5 79
?3	5 06		4 38		4 87	3 70	3 .2		4 27	3 84	3 47	3 42
4	4 33		3 68		3 97	3 82	3 63	3 29	3 80	3 65	3 44	3 16
25	5 86		4 69		5 62	5 58	4 75	3 94	5 0	5 10	4 40	4 08
6	5 30		4 0		4 62	4 60	3 62	3 37	4 ?9	4 32	4 03	3 59
7	3 39		3 08		3 06	2 64	2 99	68	3 22	2 90	2 55	2 42
28	6 36		6 30		4 3	3 80	4 97	5 21	4 28	3 91	4 28	4 40
9	2 60		3 01		2 60	2 56	2 59	2 51	2 86		2 68	
30	3 43		3 6		3 03	2 98	96	2 79	3 15	3 0	2 85	2 76

Table 9 continued PLASMA RELATIVE VISCOSITY*)

	10 C Ø 0 65 100 mmHg	10 C Ø 0 65 50 mmHg	10 C Ø 0 51 100 mmHg	10 C Ø 0 51 50 mmHg	0 C Ø 0 65 100 mmHg	0 C Ø 0 65 50 mmHg	0 C Ø 0 51 100 mmHg	0 C Ø 0 51 ?0 mmHg	37 C Ø 0 65 100 mmHg	37 C Ø 0 65 50 mmHg	37 C Ø 0 51 100 mmHg	37 C Ø 0 51 50 mmHg
18	15 45	15 50	15 70	14 72	10 07	10 06	10 02	10 00	7 60	7 47	7 39	7 35
19	6 86	6 85	6 81	6 90	6 00	5 97	5 93	5 92	5 56	5 50	5 12	5 17
0	6 30	6 35	6 18	6 14	5 ?1	5 30	4 93	5 07	5 03	5 14	4 70	4 81
21	5 98	5 87	5 63		4 73	4 7	4 74	4 67	4 56	4 46	4 40	4 36
2	7 32	7 40	7 5	7 47	4 63	4 60	4 90	4 93	3 89	3 96	3 84	3 84
23	3 44	3 30	3 21	3 12	3 00	2 93	3 01	? 94	2 9?	2 90	2 78	2 80
24	3 06	2 98	2 96	2 85	2 77	2 74	2 75	2 72	2 69	2 65	2 69	2 69
25	3 2		3 10		2 74	2 63	2 69	2 71	2 62	2 57	2 54	2 50
.6	2 92	2 69	2 70	2 6?	2 5?	2.52	2 65	2 51	2 47	2 44	2 38	2 36
27	2 35	2 3	2.33	2 28	2 17	2 17	2 18	2 15	2 43	2 36	2 37	2 37
8	2 39				2 32	2 28	2 36	2 8	2 69	2 67	2 68	2 64
29	2 04	1 85	1 91	1 87	1 88	1 85	1 83	1 78	1 95	1 88	1 86	1 82
30	1 97	1 93	1 80	1 81	1 88	1 88	1 90	1 88	1 96	1 91	1 87	1 86

) measured at three temperatures (10 ?0 and 37 C) with two capillaries of 0 65 mm and 0 51 mm diameters with positive pressures of 100 mmHg and ?0 mmHg

Table 9 continued SERUM RELATIVE VISCOSITY*)

	10 C Ø 0 65 100 mmHg	10 C Ø 0 65 50 mmHg	10 C Ø 0 51 100 mmHg	10 C Ø 0 51 50 mmHg	20 C Ø 0 65 100 mmHg	20 C Ø 0 65 50 mmHg	20 C Ø 0 51 100 mmHg	20 C Ø 0 51 50 mmHg	37 C Ø 0 65 100 mmHg	37 C Ø 0 65 50 mmHg	37 C Ø 0 51 100 mmHg	37 C Ø 0 51 50 mmHg	Serum reduced specific viscosity	TVI $\frac{\eta r\ 10\ C}{\eta r\ 37\ C} \times 100$
18	13 05	12 65	12 90		8 93	8 87	9 01	8 89	6 48	6 47	6 42	6 46	0 48	201
19	5 58	5 44	5 07	5 05	4 88	4 76	4 52	4 53	4 25	4 18	3 87	3 87	0 32	131
20	4 95	4 82	4 87	4 63	4 39	4 02	4 23	3 96	3 78	3 64	3 87	3 83	0 28	131
21	4 57	4 50	4 58	4 61	3 98	3 88	4 03	3 97	3 50	3 48	3 43	3 42	0 27	130
22	5 61	5 56	5 58	5 66	4 06	4 13	4 13	4 03	3 35	3 25	3 22	3 32	0 28	167
23	2 86	2 82	2 84	2 79	2 74	2 74	2 76	2 72	2 64	2 64	2 58	2 58	0 21	106
24	2 66	2 59	2 52	2 51	2 41	2 37	2 36	2 34	2 38	2 33	2 30	2 28	0 17	112
25	2 41	2 45	2 36	2 31	2 22	2 21	2 19	2 16	2 22	2 17	2 19	2 15	0 15	108
26	2 13	2 09	2 09	2 09	2 03	1 98	2 03	1 97	2 04	2 00	1 97	1 98	0 13	109
27	2 13	2 10	2 12	2 07	2 04	2 04	2 05	2 00	2 03	2 04	2 03	1 99	0 16	105
28	1 69	1 67	1 82	1 79	1 69	1 67	1 65	1 61	1 72	1 67	1 68	1 66	0 10	98
29	1 71	1 59	1 62	1 60	1 62	1 58	1 61	1 53	1 68	1 64	1 59	1 56	0 11	102
30	1 62	1 60	1 69	1 72	1 63	1 57	1.58	1 55	1 68	1 62	1 62	1 60	0 10	96

*) measured at three temperatures (10 20 and 37 C) with two capillaries of 0 65 mm and 0 51 mm diameters with positive pressures of 100 mmHg and 50 mmHg

Table 10 MACROGLOBULINEMIA SERIES

Case number and name	Age and sex	Hb g/100 ml	RBC x10⁶/cu mm	MCH μ g	Hct vol %	WBC /cu mm	ESR mm/h	Serum total protein concentration g/100 ml	Paper electrophoretic distribution Albumin g/100 ml	Globulins g/100 ml α_1	α_2	β	γ+M
1 TT	40 M	9 0	3 23	27	30 5	11 600	138	11 8	2 18	0 26	0 54	0 81	8 01
2 ET	60 F	9 8	3 20	30	31 5	1 400	129	10 7	2 98	0 35	0 61	0 45	6 16
3 IH	63 M	7 8	2 30	30	27 5	3 700	141	9 9	2 72	0 40	0 64	0 56	5 58
4 AK	64 M	8 7			33 5	7 800	138	9 5	3 14	0 35	0 80	0 84	4 34
5 VA	65 M	10 8	3 00	35	27 0	4 200	152	9 4	3 56	0 28	0 48	0 56	4 52
6 UV	58 M	11 2	3 70	30	38 0	6 400	45	9 3	4 13	0 29	0 89	0 63	3 37
7 JM	79 F	11 5	3 53	33	33 5	5 600	132	8 3	3 87	0 36	0 53	0 56	2 90
8 HO	64 F	13 2			40 5	5 100	121	8 4	2 91	0 53	0 75	0 81	3 40
9 JP	71 M	10 2			32 5	4 600	107	9 1	4 02	0 44	0 75	0 79	3 09
10 UK	52 M	11 0	3 62	30	34 5	5 800	129	8 2	3 86	0 29	0 47	0 54	3 04
11 TV	42 M	12 0	4 60	26	44 0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 10 continued

Albumin globulin ratio	Plasma fibrinogen concentration mg/100 ml	Immunoelectrophoresis Main immunoglobulin	Fractions in serum ultracentrifugal analysis g/100 ml X	A	G	Z	M	SIA test	Presence of cryo glob	fibrinog	Urine B J protein
1 0 72	0	M	0 6	2 7	5 7	0 4	M_1 15 0 S 2 1 M ~1 S 0 3	+++	++	—	—
2 0 39	407	γ M	0 3	3 9	0 9	—	M_1 17 0 S 5 1 M_2 22 0 S 0 5	+++	++	—	—
3 0 36	248	γ M	0 4	5 0	1 4	—	M_1 13 7 S 1 8 M_2 19 6 S 0 7	+++	—	—	—
4 0 49	414	M	0 6	3 5	1 6	—	M_1 3 8	+++	—	—	—
5 0 61	389	M	0 6	4 1	1 4	—	M_1 15 1 S 2 7 M_2 26 1 S 0 6	+++	—	—	—
6 0 79	634	γ M	0 4	5 2	2 1	—	M_1 17 3 S 1 6	+	—	—	—
7 0 87	32	M				—		+++	—	—	—
8 0 53	03	γ M	0.5	4 1	1 4	—	M_1 17 2 S [illegible]4	+++	—	—	—
9 0 80	4 5	M	0 5	5 0	1 5	—	M_1 16 9 S [illegible]1	+	—	—	—
10 0 89	391	γ M	0 5	4 4	1 3	—	M_1 17 0 S 1 6 M 24 5 S 0 3	+++	—	—	—
11 0 81	366	γ M	1 1	4 1	2 0	—	M_1 18 0 S 0 9	—	—	—	—
12 0 91	81	γ M	0 4	4 8	1 6	—	M_1 16 3 S 1 0	+	—	—	—
13 0 71	470	γ M	0 5	4 9	1 0	—	M_1 16 0 S 1 0 M_2 21 0 S 0 1	++	—	—	—
14 0 62	836	γ M	0 6	4 8	2 5	—	M_1 17 0 S 0 9	++	—	—	—
15 0 90	83	γ M	0 4	5 4	0 7	—	M_1 17 1 S 1 4 M_2 8 2 S 0 1	—	—	—	—
16 1 09	332	γ M	0 6	4 2	1 6	—	M_1 16 5 S 1 0	+	—	—	—
17 0 80	49	γ M	0 7	4 8	1 6	—	M_1 18 0 S 0 8	++	—	—	—

Table 9 continued SERUM RELATIVE VISCOSITY*)

	10 C				20 C				37 C				Serum reduced specific viscosity	TVI
	Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51			$\frac{\eta r\ 10\ C}{\eta r\ 37\ C} \times 100$
	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg		
18	13 05	12 65	12 90		8 93	8 87	9 01	8 89	6 48	6 47	6 42	6 46	0 48	201
19	5 58	5 44	5 07	5 05	4 88	4 76	4 52	4 53	4 25	4 18	3 87	3 87	0 32	131
20	4 95	4 82	4 87	4 63	4 39	4 02	4 23	3 96	3 78	3 64	3 87	3 83	0 28	131
21	4 57	4 50	4 58	4 61	3 98	3 88	4 03	3 97	3 50	3 48	3 43	3 42	0 27	130
22	5 61	5 56	5 58	5 66	4 06	4 13	4 13	4 03	3 35	3 25	3 22	3 32	0 28	167
23	2 86	2 82	2 84	2 79	2 74	2 74	2 76	2 72	2 64	2 64	2 58	2 58	0 21	106
24	2 66	2 59	2 52	2 51	2 41	2 37	2 36	2 34	2 38	2 33	2 30	2 28	0 17	112
25	2 41	2 45	2 36	2 31	2 22	2 21	2 19	2 16	2 22	2 17	2 19	2 15	0 15	108
26	2 13	2 09	2 09	2 09	2 03	1 98	2 03	1 97	2 04	2 00	1 97	1 98	0 13	109
27	2 13	2 10	2 12	2 07	2 04	2 04	2 05	2 00	2 03	2 04	2 03	1 99	0 16	105
28	1 69	1 67	1 82	1 79	1 69	1 67	1 65	1 61	1 72	1 67	1 68	1 66	0 10	98
29	1 71	1 59	1 62	1 60	1 62	1 58	1 61	1 53	1 68	1 64	1 59	1 56	0 11	102
30	1 62	1 60	1 69	1 72	1 63	1 57	1 58	1 55	1 68	1 62	1 62	1 60	0 10	96

*) measured at three temperatures (10 20 and 37 C) with two capillaries of 0 65 mm and 0 51 mm diameters with positive pressures *of 100 mmHg and 50 mmHg*

Table 10 *MACROGLOBULINEMIA SERIES*

Case number and name	Age and sex	Hb g/100 ml	RBC x10⁶/cu mm	MCH μ g	Hct vol %	WBC /cu mm	ESR mm/h	Serum total protein concentration g/100 ml	Paper electrophoretic distribution: Albumin g/100 ml	Globulins g/100 ml α_1	α_2	β-	γ+M-
1 TT	40 M	9 0	3 23	27	30 5	11 600	138	11 8	2 18	0 26	0 54	0 81	8 01
2 ET	60 F	9 8	3 [illegible]0	30	31 5	1 400	129	10 7	2 98	0 35	0 61	0 45	6 16
3 III	63 M	7 8	2 30	30	27 5	3 700	141	9 9	2 72	0 40	0 64	0 56	5 58
4 AK	64 M	8 7			33 5	7 800	138	9 5	3 14	0 35	0 80	0 84	4 34
5 VA	65 M	10 8	3 00	35	27 0	4 200	152	9 4	3 56	0 28	0 48	0 56	4 52
6 UV	58 M	11 2	3 70	30	38 0	6 400	45	9 3	4 13	0 29	0 89	0 63	3 37
7 JM	79 F	11 5	3 55	33	33 5	5 600	132	8 3	3 87	0 36	0 53	0 56	2 90
8 HO	64 F	13 2			40 5	5 100	121	8 4	2 91	0 53	0 75	0 81	3 40
9 JP	71 M	10 2			32 5	4 600	107	9 1	4 02	0 44	0 75	0 79	3 09
10 UK	52 M	11 0	3 62	30	34 5	5 800	129	8 2	3 86	0 29	0 47	0 54	3 04
11 TV	42 M	12 0	4 60	26	44 0	7 700	92	8 1	3 62	0 28	0 57	0 59	3 05
12 FE	56 M	15 6	4 90	32	48 5	5 400	97	7 8	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
13 LC	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

9	3 74	3 7	3 63	3 63	3 46	3 36	3 40	3 30	3.24	3 08	3 08	3 08
10	3.25	3 19	3 02	3 01	2 93	2 89	2 93	2 89	78	2 74	2 70	2 71
11	3 03	3 02	2 90	2 86	2 70	2 68	2 80	2 72	2 80	2 82	2 85	2 85
12	3 00	2 91	2 85	2 85	2 73	2 71	2 72	2 67	2 78	2 72	2 55	2 54
13	2 98	2 92	2 80	2 84	2.27	2 4	2.26	2 21	2 80	2 80	2 62	2 63
14	4 55	4 72	4.57	4 67	3 53	3 45	3 43	3 33	3 31	3 17	3 0	3 11
15	2 48	2 5	2 39	2 39	2 38	38	2 34	2 28	2 44	2 40	2.31	2 34
16	2 54	51	2 42	2 47	2 46	2 43	2 38	2 8	2 38	2 37	2 31	2 30
17	2 6	2 77	2 66	2 68	2 47	2 47	2 52	2 50	2 51	2 48	2 31	2 31

Table 10 continued SERUM RELATIVE VISCOSITY)

	10 C				20 C				37 C				Serum reduced specific viscosity	TVI r 10 C / r 37 C × 100
	⌀ 0 65		⌀ 0 51		⌀ 0 65		⌀ 0 51		⌀ 0 65		⌀ 0 51			
	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg		
1	15 12	16 30	18 61	22 70	9 59	9 41	9 14	8 67	7 72	7 57	7 57	7 39	0 57	196
2	11 35	14 40	9 15	9 0	9 31	9 02	7 80	7 72	5 37	5 44	5 47	5 53	0 41	211
3	5 58	5 36	5 36	5 31	5 09	5 12	5 07	4 97	5 14	5 09	5 0	5 07	0 42	109
4	9 53	9 14	8 80	8 77	6 53	6 48	6 55	6.35	4 97	4 82	4 72	4 75	0 42	192
5	4 0	4 07	3 83	3 72	3 50	3 44	3 60	3 55	3 40	3 30	3 32	3.27	0 6	118
6	3 20	3 05	5 09	4 88	3 56	3 58	3 45	3 29	3 20	3 09	2 96	2 82	0 24	103
7	3 84	3 76	3 79	3 78	3 55	3 44	3 48	3 52	3 08	3 07	2 93	2 93	0 5	125
8	2 89	2 85	2 88	2 84	2 91	2 88	2 64	2 55	2 72	2 72	2 56	2 53	0 21	106
9					2 82	2 76	2 69	2 68	2 71	2 57	2 57	2 54	0 19	
10	2 78	2 74	.79	2 79	2 74	2 73	2 69	2 70	2 65	2 67	2 56	[illegible]	0 20	105
11	2 63	2 57	2 47	2 55	2 51	2 48	2 5	2 30	2 51	2 46	2 37	2 36	0 19	105
12	2 69	2 66	2 54	2 50	2 52	2 48	2 48	2 44	2 49	2 43	2 36	2 31	0 19	108
13	2 42	38	.40	2 34	2 74	2 70	2 74	2 59	2 36	2 6	2 19	2.20	0 18	107
14	3 07	3 02	3 09	2 99	2 82	2 82	2 80	2 70	2 35	2 42	2 32	2 34	0 15	131
15	2 14	2 06	2 10	2 14	2 13	2 06	2 05	2 03	2 21	2 14	2 15	2 15	0 15	97
16	2 21	2.23	2 16	2 16	2 18	2 19	2 13	2 11	2 11	08	2 18	2 18	0 15	105
17	2 18	2 11	2 05	2 01	2 03	1 99	2 00	1 97	2 04	2 03	1 93	1 90	0 13	107

) measured at three temperatures (10 0 and 37 C) with two capillaries of 0 65 mm and 0 51 mm diameters with positive pressures of 100 mmHg and 50 mmHg

Table 10 continued BLOOD RELATIVE VISCOSITY)

	10 C				20 C				37 C			
	Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51	
	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg
1	39 40		62 50		17 90	17 05	14 55	12 69	13 60	12 32	12 00	11 93
2	24 00		19 00		19 50	15 88	13 81	12 28	7 58	7 15	9 67	7 60
3	10 00		10 01		8 87	8 42	7 87	7 32	8 03	8 02	7 40	7 06
4	19 95		19 55		12 90	13 30	11 80	11 45	8 50	8 31	7 57	7 42
5	7 49		7 01		7 17	7 10	6 57	5 83	6 62	6 62	6 17	6 34
6	13 15		11 45		9 39	9 09	8 61	7 85	7 00	6 84	6 87	6 88
7	6 86		7 11		5 16	5 28	5 10	4 62	6 18	5 51	5 92	4 89
8	8 62		8 56		6 54	5 78	5 28	5 24	6 17	5 84	5 37	4 52
9	7 92		7 16		6 02	6 06	5 41	5 07	5 03	5 04	4 91	4 31
10	6 63		5 56		7 63	6 45	5 54	4 84	5 72	5 19	4 60	4 31
11	7 55		6 71		6 64	6 36	5 30	4 55	6 17	5 92	5 62	4 72
12	6 55		5 90		6 32	5 90	5 17	4 62	5 75	5 33	4 29	4 02
13	4 70		4 14		4 18	4 06	3 72	3 44	3 90	3 65	3 32	3 04
14	9 22		8 80		7 64	7 63	7 16	6 14	6 56	6 33	5 92	5 43
15	5 12		4 44		4 91	4 71	4 53	4 37	4 22	4 31	3 90	3 86
16	6 08		5 56		5 53	5 74	4 88	4 00	4 78	4 63	4 61	3 88
17	6 23		4 57		5 32	5 12	4 28	3 71	4 72	4 62	4 22	3 88

Table 10 continued PLASMA RELATIVE VISCOSITY *)

	10 C				20 C				37 C			
	Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51	
	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg
1	26 60	25 80	24 60	29 20	11 95	11 65	12 00	11 70	9 52	9 38	9 07	8 86
2	22 90	23 39	21 58	23 41	14 00	13 14	13 60	13 30	9 18	9 15	9 50	9 15
3	6 77	6 65	6 18	6 00	5 94	5 82	6 18	5 73	5 52	5 40	5 57	5 75
4	13 00	12 45	12 20	12 20	8 75	8 60	8 20	8 20	6 17	6 10	6 07	6 09
5	4 70	4 62	4 63	4 52	4 30	4 29	4 33	4 48	4 17	4 10	4 27	4 17
6	6 08	5 87	5 77	6 13	4 [illegible]2	4 43	4 37	4 27	3 89	3 78	3 72	3 64
7	4 33	4 32	4 25	4 37	4 26	4 16	4 06	4 02	3 58	3 [illegible]4	3 52	3 [illegible]1
8	3 51	3 74	3 30	3 28	3 06	3 02	3 22	3 14	3 15	2 99	2 88	2 85

12	4 33		5 13		5 7	4 61	4 61		4 58	4 47	4 18	
13	7 77		6 86		6 45	6 31	5 98	5 15	6 13	5 90	5 55	5 05
14	6.32		6.37		5.23	5 82	5 88	5 48	5 12	5 24	5 17	5 12
15	6 84		6 74		6 34	6 64	5 34	5 0	5 87	6 05	5 80	5 07
16	6.22		5 7?		4 88	4 87	4 39	3 84	4 97	4 83	5 07	4 13
17	6 99		6 74		6 34	6 47	6 01	5 47	5 48	5 54	5.51	4 88
18	7 13		6 98		6 04	6 07	5.22	4 9?	5 75	5 63	5 45	4 91
19	6 54		4 9?		5 9?	5 75	5 57		5 39	5 46	5 33	5 00
?0	6 13		5 78		3 f6	5 96	5 36	5 64	5 0	5 17	4 9?	5 07
1	6 02		5 79		3 61	5 69	5 05	4 83	5 07	4 94	4 78	4 48
?2	7_0		6 89		6 83	6 80	5 81	5 70	5 94	5 78	5 53	● 5 38

Table 11 continued PLASMA RELATIVE VISCOSITY)

	10 C				?0 C				37 C			
	O 0 65		O 0 51		O 0 65		Ø 0 51		Ø 0 65		Ø 0 51	
	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	?0 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg
1	• 65	60	_ 60	2 65	2 46	2 45	2 42	2 40	2 43	2 37	2 7	2.25
2	2 54	48	2 37	2 33	2..9	2 27	..9	2.28	2 41	2 41	2 ?8	2 8
3	2 73	2 77	2 57	2 54	2 45	2 44	2 47	2 42	2 51	2 47	2 49	2 46
4	2 08	2 88	2 87	2 94	2 77	2 72	2 67	? 59	2 72	2 74	2 61	2 63
5	2 48	2 48	2 45	2 42	2 34	2 35	2 37	2 3?	? 39	29	2 .6	? 26
6	2 67	2 61	6_	2 58	2 44	2 39	2 45	2 40	2 78	2 74	2 9	2 60
7	2 60	2 62	2 58	2 32	47	2 43	2 40	2 36	2 38	2 35	2 33	2 34
8	3 3..	3 6	3 07	3 07	3 00	3 03	3 10	3 07	3 18	98	2 96	2 95
9	• 64	2 59	2 59	2 58	2 50	2 47	2 30	2 6	2 48	2 38	• 36	2 36
10	69	2 65	2 56	2 57	2 46	2 49	50	2 46	2 54	2 47	2 45	2 48
11	2 09	3 0?	2 67	2 67	2 46	2 42	? 46	2 40	2 64	2 60	2 47	? 46
12	2 93	? 88	83	2 83	2 68	2 66	66	2 64	2 70	2 64	2 67	67
13	3 38	3 36	3 ??	3 17	2 ?	2 88	3 11	2 99	2 99	2 91	2 84	2 8?
14	? 73	80	2 60	79	2 72	2 68	2 64	2 55	2 68	2 63	2 54	2 54
15	3 12	3 1_	? 86	? 85	2 62	2 8	2 65	2 60	2 85	2 76	2 72	2 73
16	• 90	3 02	2 93		? 71	? 69	2 62	2 6?	2 70	2 66	2 61	2 56
17	3 00	2 93	2 94	? 90	2 82	2 8?	81	2 78	2 81	2 78	. 62	2 68
18	? 83	2 73	2 70	2 56	2 60	2 54	2 64	2 60	2 6	2 0	2 48	2 0
19	3 18	3 17	3 7	3 30	2 61	2 58	2 59	? 51	2 67	2 60	2 .6	50
0	2 88	84	2 60	? 6	? 49	2 50	2 55	2 40	2 51	2 48	2 49	2 47
1	4 03	4 08	3 74	3 82	3 59	3 .8	3 45	3 44	3 53	3 4?	3 0	3 47
?	4 17	4 00	3 91	3 80	3 68	3 61	3 61	3 56	3 59	3 56	3 49	3 43

) measured at three temperatures (10 0 and 37 C) with two capillaries of 0 65 mm and 0 51 mm diameters with positive pressures of 100 mmHg and 50 mmHg

Table 11 ANKYLOSING SPONDYLITIS SERIES

Case number and name	Age and sex	Hb g/100 ml	RBC x10⁶/cu mm	MCH μ g	Hct vol %	WBC /cu mm	ESR mm/h	Serum total protein conc g/100 ml	Paper electrophoretic distribution Albumin g/100 ml	Globulins g/100 ml α_1-	α_2-	β	γ-	Albumin globulin ratio	Plasma fibrinogen concentration mg/100 ml	SIA test	Presence of cryo- globulin	fibrinogen
1 IK	31 F	13 1	4 60	29	40 0	8 400	62	8 4	4 27	0 24	0 66	0 98	2 24	1 03	534	—	—	—
2 PS	29 M	12 7	4 52	28	32 0	5 500	59	7 7	3 44	0 40	1 03	1 13	1 71	0 81	557	+	—	—
3 PK	44 M	12 0	4 35	27	45 0	7 700	48	8 1	4 30	0 28	0 78	1 18	1 57	1 14	556	—	—	—
4 LL	51 M	13 8	4 60	30	37 5	5 400	66	8 2	3 95	0 36	0 81	0 94	2 14	0 93	615	+	—	—
5 TR	19 M	10 6	3 80	28	38 0	7 700	95	7 9	3 72	0 43	1 04	1 11	1 57	0 89	499	—	—	—
6 LK	44 M	12 0	4 90	25	41 5	13 000	76	7 2	2 98	0 40	0 99	1 09	1 74	0 72	622	—	—	—
7 HL	58 M	14 0	4 50	32	45 0	6 000	46	8 2	3 95	0 34	0 64	1 07	2 20	0 93	473	—	—	—
8 VS	39 M	12 0	4 25	28	33 0	6 300	111	8 5	3 80	0 70	0 98	1 09	1 93	0 81	656	—	—	—
9 KL	39 M	14 0	4 90	29	39 5	6 100	54	7 9	3 95	0 31	0 77	0 98	0 89	1 01	473	—	—	—
10 MK	24 M	13 7	4 60	30	37 0	5 500	46	8 7	4.30	0 34	1 00	1 26	1 80	0 97	520	—	—	—
11 OP	49 M	12 0	3 90	30	40 0	5 500	72	7 8	3 80	0 39	0 94	1 10	1 57	0 94	563	—	—	—
12 VI H	57 M	9 4	3 30	28	35 0	9 700	124	7 6	2 46	0 28	1 06	0 84	2 98	0 47	645	—	—	—
13 LK	44 M	13 0	4 40	30	43 5	5 200	85	8 7	3 91	0 42	1 04	1 17	2 12	0 81	844	+	—	—
14 TJ	44 M	13 0	4 40	29	46 5	7 800	39	8 2	4 00	0 32	0 76	1 13	1 98	0 96	512	+	—	—
15 VS A	58 M	12 7	4 54	28	45 0	5 400	69	8 9	3 88	0 39	0 80	0 95	2 89	0 76	596	+	—	—
16 ML	49 F	11 1	3 97	28	37 0	8 400	62	8 2	3 70	0 35	0 97	1 03	2 19	0 82	615	—	—	—
17 RS	30 M	12 7	4 55	28	38 0	6 500	71	8 7	3 96	0 43	1 03	0 91	2 36	0 84	547	+	—	—
18 MM	54 M	13 5	4 70	29	47 0	5 700	62	8 2	3 60	0 33	1 15	1 03	2 10	0 78	436	+	—	—
19 AS	53 M	12 0	4 10	29	41 0	6 000	98	8 4	3 55	0 46	0 89	1 23	2 28	0 74	662	—	—	—
20 AJ	36 M	10 5	3 90	27	29 5	8 600	82	8 6	3 07	0 58	0 94	1 00	3 11	0 56	586	—	—	—
21 TL	27 M	12 0	4 30	28	32 5	6 200	121	8 7	3 43	0 65	1 17	1 24	2 22	0 65	818	—	—	—
22 JL	39 M	11 6	4 50	26	33 0	7 500	122	9 4	2 85	0 40	0 98	0 99	4 18	0 43	672	—	—	—

Table 11 continued BLOOD RELATIVE VISCOSITY *)

	10 C Ø 0 65 100 mmHg	50 mmHg	Ø 0 51 100 mmHg	50 mmHg	20 C Ø 0 65 100 mmHg	50 mmHg	Ø 0 51 100 mmHg	50 mmHg	37 C Ø 0 65 100 mmHg	50 mmHg	Ø 0 51 100 mmHg	50 mmHg
1	6 51		5 93		5 34	3 37	5 00	4 53	4 79	4 62	4 61	4 16
2	4 74		4 03		4 89	4 19	3 55	3 49	3 84	3 86	3 60	3 34
3	5 50		6 15		5 59	5 53	5 14	4 94	4 91	4 87	4 47	4 46
4	8 17		7 25		6 54	6 75	6 32	5 34	6 54	6 42	6 09	5 57
5	7 16		6 23		6 23	5 68	5 30	5 11	5 32	4 98	4 82	4 20
6	6 83		6 07		5 73	5 52	4 94	4 17	4 99	4 86	4 49	4 18
7	6 45		5 66		5 84	5 68	4 98	4 38	5 25	5 13	4 50	4 28
8	8 16		7 32		6 80	6 87	6 36	6 47	6 32	6 27	6 10	5 64
9	7 35		6 40		6 15	5 66	5 32	5 12	6 34	6 15	5 17	4 37
10	7 10		6 92		6 50	6 50	6 13	5 43	6 01	5 74	5 59	5 39
11	5 95		5 05		5 48	5 52	5 12	4 40	5 12	4 95	4 87	4 28

12	4 33		5 13		5 7	4 61	4 61		4 58	4 47	4 18	
13	7 77		6 80		6 45	6 31	5 98	5 15	6 13	5 96	5 55	5 03
14	6.32		6.37		5..3	5 8	5 88	5 48	5 12	5..4	5 17	5 12
15	6 84		6 74		6 34	6 64	5 34	5 02	5 87	6 05	5 80	5 07
16	6.22		5 7?		4 88	4 87	4 39	3 84	4 97	4 83	5 07	4 13
17	6 99		6 74		6 34	6 47	6 01	5 47	5 48	5 54	5 51	4 88
18	7 13		6 98		6 04	6 07	5 22	4 9?	5 75	5 63	5 45	4 91
19	6 54		4 9?		5 9?	5 75	5 57		5 39	5 46	5 33	5 00
0	6 13		5 78		5 66	5 98	5 36	3 64	5 02	5 17	4 9	5 07
21	6 0		5 79		5 61	5 69	5 05	4 83	5 07	4 94	4 78	4 48
2	7 0		6 89		6 83	6 80	5 81	5 70	5 94	5 78	5 53	5 38

Table 11 continued PLASMA RELATIVE VISCOSITY)

	10 C				?0 C				37 C			
	Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51	
	100 mmHg	.0 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	0 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg
1	2 65	2 60	* 60	2 65	2 46	2 45	2 42	2 40	2 43	2 37	2.27	2 5
2	2 54	2 48	2.37	2 33	2 9	2 27	2 29	2 8	2 41	2 41	2 28	2 8
3	2 73	2 77	2 57	2 54	2 45	2 44	2 47	2 42	2 51	2 47	2 49	2 40
4	2 98	2 88	2 87	2 94	2 77	2 72	2 67	2 59	2 72	2 74	2 61	2 63
5	2 48	2 48	2 45	2 42	2 34	2 35	2 37	2 32	2 39	2 29	26	2 6
6	2 67	2 61	2 62	2 58	* 44	2 39	2 45	2 40	2 78	2 74	2 59	2 60
7	- 60	2 6-	2.58	2 5?	2 47	2 43	2 40	36	2 38	2 35	2 33	2 34
8	3 32	3 6	3 07	3 07	3 00	3 03	3 10	3 07	3 18	2 98	2 96	2 95
9	2 64	59	* 59	2 58	2 50	2 47	2 30	2 *6	2 48	2 38	2 36	2 36
10	69	2 65	2 56	2 57	2 46	2 49	2 50	2 46	2 54	2 47	2 45	2 48
11	2 08	3 0	* 67	2 67	2 46	* 42	2 46	2 40	2 64	2 60	2 47	2 46
12	* 9	* 88	2 83	2 83	2 68	2 60	2 66	2 64	2 70	2 64	2 67	2 67
13	3 38	3 36	3	3 17	2 9?	2 88	3 11	2 09	2 09	* 91	2 84	2 8?
14	- 73	2 80	2 00	* 79	2 72	2 68	2 64	2 55	2 68	* 63	2 54	2 54
15	3 12	3 12	2 86	2 85	2 62	2 8	2 65	2 60	2 85	2 76	2 72	73
16	- 90	3 0	2 93		2 71	2 69	2 62	2 62	2 70	2 68	2 61	2 56
17	3 00	2 93	2 94	2 96	2 8	2 82	2 81	2 78	2 81	2 78	2 62	2 68
18	2 83	73	2 70	2 56	* 60	2 54	2 64	2 60	2 56	* 50	2 48	2 50
19	3 18	3 17	3 7	3 30	2 61	2 58	2 59	2 51	2 67	2 60	* 56	2 50
0	2 88	2 84	* 60	2 62	* 49	2 50	2 55	2 49	2 51	2 48	2 49	2 47
21	4 03	4 08	3 74	3 82	3 59	3 58	3 45	3 44	3 53	3 42	3 0	3 47
"	4 17	4 00	3 91	3 80	3 68	3 61	3 61	3 56	3 59	3 50	3 49	3 43

) measured at three temperatures (10 0 and 37 C) with two capillaries of 0 65 mm and 0 51 mm diameters with positive pressures of 100 mmHg and 50 mmHg

Table 11 continued SERUM RELATIVE VISCOSITY *)

	10 C Ø 0 65 100 mmHg	10 C Ø 0 65 50 mmHg	10 C Ø 0 51 100 mmHg	10 C Ø 0 51 50 mmHg	20 C Ø 0 65 100 mmHg	20 C Ø 0 65 50 mmHg	20 C Ø 0 51 100 mmHg	20 C Ø 0 51 50 mmHg	37 C Ø 0 65 100 mmHg	37 C Ø 0 65 50 mmHg	37 C Ø 0 51 100 mmHg	37 C Ø 0 51 50 mmHg	Serum reduced specific viscosity	TVI $\frac{\eta r\ 10\ C}{\eta r\ 37\ C} \times 100$
1	2 12	2 15	2 07	2 08	2 02	2 01	2 00	1 94	1 87	1 88	1 97	1 95	0 10	113
2	2 10	2 04	2 06	2 05	1 93	1 93	1 93	1 93	1 97	1 91	1 87	1 86	0 13	107
3	2 05	2 04	1 97	1 96	1 96	1 93	1 93	1 89	1 99	1 95	1 92	1 90	0 12	103
4	2 21	2 18	2 19	2 16	2 08	2 08	2 08	2 05	1 99	2 06	2 14	2 10	0 12	111
5	2 19	2 15	2 06	2 02	2 01	2 00	2 04	2 01	2 06	2 04	1 97	1 96	0 13	110
6	2 09	2 04	2 03	1 99	1 99	1 94	1 94	1 94	2 07	1 96	1 89	1 86	0 15	101
7	2 10	2 05	1 99	2 00	2 02	1 95	1 95	1 90	2 07	1 99	1 93	1 92	0 13	101
8	2 10	2 06	2 06	1 98	1 99	1 95	2 07	2 07	2 08	2 08	2 10	2 09	0 13	101
9	2 16	2 15	2 02	2 05	2 06	2 06	1 98	1 95	2 09	2 04	1 98	1 99	0 14	103
10	2 27	2 27	2 16	2 16	2 12	2 11	2 09	1 97	2 10	2 10	2 04	2 04	0 13	108
11	1 99	1 95	2 00	1 95	1 96	1 90	1 91	1 88	2 10	2 06	1 95	1 85	0 14	95
12	2 21	2 23	2 20	2 16	2 10	2 06	2 06	2 00	2 11	2 11	2 05	2 04	0 15	105
13	2 30	2 31	2 31	2 26	2 22	2 18	2 15	2 12	2 14	2 08	2 15	2 14	0 13	107
14	2 27	2 17	2 16	2 15	2 10	2 05	2 16	2 15	2 14	2 11	2 06	2 04	0 14	106
15	2 27	2 27	2 19	2 18	2 20	2 18	2 14	2 12	2 19	2 17	2 12	2 05	0 13	104
16	2 20	2 18	2 20	2.20	2 11	2 08	2 06	2 03	2 19	2 16	2 00	1 98	0 15	100
17	2 30	2 28	2 26	2 24	2 18	2 14	2 18	2 12	2 23	2 21	2 12	2 12	0 14	103
18	2 23	2 23	2 16	2 09	2 06	2 04	2 10	2 02	2 26	2 21	2 05	2 01	0 15	99
19	2 42	2 40	2 39	2 33	2 34	2 27	2 28	2 22	2 31	2 28	2 24	2 23	0 16	105
20	2 38	2 33	2 29	2.25	2 16	2 14	2 17	2 13	2 32	2 20	2 19	2 16	0 15	103
21	2 73	2 80	2 78	2 75	2 62	2 61	2 57	2 55	2 [illegible]8	2 61	2 54	2 54	0 18	106
22	2 84	2 80	2 87	2 78	2 62	2 67	2 68	2 62	2 75	2 66	2 [illegible]8	2 58	0 19	107

*) measured at three temperatures (10 20 and 37 C) with two capillaries of 0 65 mm and 0 51 mm diameters with positive pressures of 100 mmHg and 50 mmHg

Table 12 CONTROL SERIES

Case number and name	Age and sex	Hb g/100 ml	RBC x10⁶/cu mm	MCH μμg	Hct vol %	WBC /cu mm	ESR mm/h	Serum total protein conc g/100 ml	Paper electrophoretic distribution Albumin g/100 ml	Globulins α_1	α_2	g/100 ml β	γ	Albumin globulin ratio	Plasma fibrinogen concentration mg/100 ml	SIA test	Presence of cryo globulin	Presence of cryo fibrinogen
1 TS	28 M	15 7	5 29	29	49 0	5 300	7	7 5	4 77	0 21	0 57	0 75	1 20	1 76	261	—	—	—
2 TP	35 F	12 7	4 40	29	42 5	6 900	14	6 8	4 15	0 18	0 37	0 80	1 17	1 69	376	—	—	—
3 EP	49 M	15 6	5 20	30	50 0	6 100	6	7 2	4 23	0 33	0 62	0 78	1 19	1 43	326	—	—	—
4 VR	42 F	14 0	4 65	30	42 5	4 100	7	7 2	4 03	0 21	0 48	0 74	1 74	1 28	296	--	—	—
5 IE	70 F	14 6	4 90	30	43 0	4 300	14	7 7	3 89	0 30	0 76	0 99	1 71	1 06	362	—	—	—
6 VR	69 M	14 9	5 30	28	45 0	7 300	4	7 6	4 45	0 28	0 [illegible]5	0 83	1 49	1 42	326	—	—	—
7 KF	[illegible]3 M	14 2	4 90	27	47 0	7 [illegible]00	7	7 2	4 22	0 28	0 64	0 88	1 18	1 43	3[illegible]6	—	—	—
8 EH	31 F	12 4	4 30	28	37 5	4 400	9	7 5	4 47	0 2[illegible]	0 50	0 91	1 37	1 48	252	—	—	—
9 AL	76 F	12 4	4 3[illegible]	28	40 0	4 700	12	7 1	3 80	0 26	0 66	1 00	1 43	1 17	240	—	—	—

10 MR	27 M	14 9	5 00	30	49 0	6 900	6	7 4	4 66	0 20	0 41	0 87	1..7	1 69	..37	—	—	—
11 AL	9 M	14 6	4 85	30	46 0	5 900	3	7.3	4 45	0..6	0 46	0 86	1..8	1 55	243	—	—	—
12 RS	37 F	12 8	4.57	..8	41 0	4 500	4	6 9	4 49	0.23	0 46	0 66	1 04	1 90	182	—	—	—
13 VM	24 M	16 5	5.28	8	46 5	5 100	5	7 8	5 37	0 24	0 46	0 75	1 03	2 11	?25	—	—	—
14 AP	38 F	13 6	4.29	30	44 0	6 000	8	7 3	4 67	0 30	0 58	0 68	1 07	1 80	301	—	—	—
15 JN	61 M	15 7	5 35	29	0 0	9 700	14	7 9	4 48	0 39	0 65	1 04	1 34	1 33	397	—	—	—
16 HH	74 F	12 4	4.50	8	41 5	6 100	7	7 6	4 08	0.27	0 58	0 98	1 69	1 16	261	—	—	—
17 VT	48 M	13 7	4 96	7	43.5	4 700	9	8 0	4 63	0 18	0 53	1 00	1 63	1 35	270	—	—	—
18 VK	35 M	13 2	4 80	27	45 0	6..00	7	7 9	4 38	0 30	0 57	0 98	1 67	1 24	334	—	—	—
19 HM	62 F	13.5	4 62	?9	44 0	4 300	15	7 7	4.27	0.29	0 55	1 06	1.53	1 24	289	—	—	—
0 LL	76 F	14 6	4 95	29	47 0	6 00	11	7 9	4.27	0 31	0 78	0 80	1 74	1 18	410	—	—	—
21 SS	34 M	13 1	4 80	27	42 0	4 800	6	7 9	4 92	0..3	0 60	0 84	1 31	1 66	275	—	—	—
22 TM	27 F	13.2	4 52	30	41 5	5 800	7	7 8	4 61	0 28	0 59	0 8?	1 50	1 46	246	—	—	—
3 FS	73 M	14.2	4 65	30	43 5	7 400	13	8 3	4 48	0 35	0 76	1 05	1 65	1 19	319	—	—	—
24 JW	76 M	15 3	5 60	28	49 0	8 300	20	8 2	4 0?	0 35	0 92	1 16	1 75	0 97	380	—	—	—

Table 12 continued BLOOD RELATIVE VISCOSITY)

	10 C				0 C				37 C			
	Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51	
	100 mmHg	0 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	0 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg
1	7 03		7 13		6 20	6 00	6 00		5 40	5 53	5 54	5 41
2	5 47		5.35		4 78	4 82	4 66	4 35	4 34	4 49	3 83	3 74
3	7 04		6 97		6 24	6 37	5 7	5 74	5 94	6 02	5 45	5 23
4	5 64		5 41		4 55	4 80	4 65	4 40	4 47	4 39	4 20	4 0?
5	6 73		5 93		4 87	5 05	5 7	5 78	5 71	5 52	4 8?	4 51
6	6 04		6 00		5 07	6 16	5 37	5 97	5 21	5 ?3	4 ?3	5 12
7	6 77		6 19		5 19	5 23	5 11	5 25	4 80	4 85	4 69	4 07
8	5 03		4 76		3 86	4 44	3 93	3 81	3 06	4 11	3 94	4 36
9	5 7		4 71		4 42	4 ?6	3 77	3 67	4 03	4 12	3 70	3 61
10	6 59		6 36		5 53	5 51	5 11	5 0	5 37	5 27	5 05	4 95
11	6 85		6 18		5 34	5 85	5 70	4 88	4 94	5 22	4 13	4 37
12	5 10		5 05		4 70	4 74	4 37	4 52	3 9	4 12	4 01	4 01
13	6 ?3		6 07		5 34	5 45	5 28	5 34	5 27	5 23	4 55	4 72
14	5 77		5 0		5 31	5 58	4 95	4 95	4 07	?15	5 03	4 87
15	7 67		7 62		6 40	6 54	5 70	6 05	5 67	5 88	6 04	5 48
16	5 86		5 6?			4 96	4 52	4 60	4 33	4 44	4 27	4.22
17	6 05		6 05		5 00	5 8	4 87	4 68	5 12	5 17	4 74	4 77
18	6 35		6 04		5 57	5 72	5 8	5 17	5 13	5 18	4 53	4 65
19	6 71		6 31		7 07	9 08	7 33	9 6	5 78	6 69	5 33	5 89
?0	6 96		5 97		5 43	5 53	5 03	4 93	5 01	4 93	4 32	4 49
1	6 0		5 65		5 57	5 88	4 53		5 06	5 20	4 10	4 14
?2	5 48		5 2		4 62	4 69	4 5	4 00	4 32	4 25	4 12	4 02
?3	6 4		6 10		5 70	5 62	4 75	4 53	5 53	5 69	5 12	5 21
24	8 01		6 93		7 45	8 18	5 55	5 0	6 51	6 54	6 16	6 26

) measured at three temperatures (10 0 and 37 C) with two capillaries of 0 65 mm and 0 51 mm diameters with positive pressures of 100 mmHg and 50 mmHg

Table 12 continued PLASMA RELATIVE VISCOSITY *)

	10 C				20 C				37 C			
	Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51		Ø 0 65		Ø 0 51	
	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg	100 mmHg	50 mmHg
1	2 01	1 98	1 89	1 89	1 91	1 83	1 87	1 82	1 97	1 90	1 86	1 78
2	2 10	2 14	2 10	1 98	2 04	1 95	1 93	1 93	2 04	2 03	1 91	1 91
3	2 06	2 06	1 92	1 88	1 93	1 93	1 89	1 88	2 00	1 96	1 96	1 94
4	2 06	2 03	2 04	1 99	1 94	1 94	1 92	1 89	1 99	1 98	1 89	1 91
5	2 28	2 30	2 16	2 18	2 06	2 04	2 05	2 00	2 11	2 10	2 00	2 01
6	2 04	2 00	1 91	1 91	1 93	1 94	1 93	1 94	2 00	1 95	1 89	1 89
7	2 14	2 10	1 95	1 97	1 95	1 95	1 97	1 93	2 00	1 92	1 91	1 90
8	2 14	2 12	2 04	2 04	1 99	1 97	1 96	1 92	2 04	2 02	1 96	1 95
9	2 12	2 07	2 01	1 99	1 97	1 9[illegible]	1 93	1 92	1 97	1 97	1 98	1 95
10	2 22	2 22	1 96	1 94	1 88	1 84	1 85	1 82	2 04	1 96	1 94	1 92
11	2 11	2 09	2 04	2 02	2 01	1 9[illegible]	1 93	1 97	2 06	2 03	1 91	1 91
12	2 01	1 93	1 89	1 86	1 91	1 87	1 84	1 82	1 90	1 85	1 81	1 82
13	2 00	1 96	1 98	1 97	1 95	1 93	1 91	1 88	2 02	1 98	1 93	1 91
14	2 00	1 95	1 94	1 88	1 89	1 86	1 89	1 84	2 02	1 96	1 90	1 87
15	2 26	2 24	2 27	2 22	2 31	2 28	2 26	2 21	2 34	2 33	2 25	2 24
16	2 21	2 16	2 21	2 19	2 17	2 10	2 11	2 02	2 07	2 00	2 01	1 94
17	2 24	2 18	2 18	2 16	2 16	2 11	2 12	2 09	2 20	2 14	2 14	2 06
18	2 26	2 42	2 15	2 06	2 08	2 04	2 05	1 98	2 14	2 11	2 14	2 12
19	2 07	2 09	2 20	2 25	2 14	2 12	2 12	2 10	2 10	2 07	2 07	2 04
20	2 33	2 28	2 22	2 25	2 13	2 07	2 10	2 04	2 22	2 16	2 23	2 19
21	2 12	2 04	2 05	2 06	2 00	1 98	1 98	1 95	2 14	2 04	2 06	2 04
22	2 12	2 14	2 08	2 14	2 10	2 08	2 08	2 04	2 07	2 05	1 96	1 98
23	2 45	2 32	2 18	2 18	2 19	2 14	2 19	2 15	2 31	2 22	2 34	2 30
24	2 [illegible]2	2 45	2 39	2 33	2 36	2 29	2 41	2 37	2 44	2 34	2 41	2 42

*) measured at three temperatures (10 20 and 37 C) with two capillaries of 0 65 mm and 0 51 mm diameters with positive pressures of 100 mmHg and 50 mmHg

Table 12 continued SERUM RELATIVE VISCOSITY *)

	10 C Ø 0 65 100 mmHg	10 C Ø 0 65 50 mmHg	10 C Ø 0 51 100 mmHg	10 C Ø 0 51 50 mmHg	20 C Ø 0 65 100 mmHg	20 C Ø 0 65 50 mmHg	20 C Ø 0 51 100 mmHg	20 C Ø 0 51 50 mmHg	37 C Ø 0 65 100 mmHg	37 C Ø 0 65 50 mmHg	37 C Ø 0 51 100 mmHg	37 C Ø 0 51 50 mmHg	Serum reduced specific viscosity	TVI r 10 C / r 37 C × 100
1	1 79	1 79	1 67	1 67	1 67	1 63	1 65	1 63	1 71	1 69	1 66	1 67	0 10	105
2	1 76	1 74	1 67	1 68	1 63	1 64	1 63	1 61	1 78	1 73	1 67	1 66	0 11	99
3	1 83	1 8_	1 83	1 81	1 77	1 73	1 76	1 75	1 78	1 72	1 67	1 65	0 11	103
4	1 79	1 77	1 75	1 76	1 67	1 68	1 72	1 70	1 78	1 79	1 71	1 71	0 11	100
5	1 89	1 89	1 83	1 80	1 86	1 81	1 78	1 73	1 79	1 81	1 77	1 81	0 10	106
6	1 81	1 76	1 77	1 74	1 80	1 76	1 76	1 73	1 81	1 78	1 82	1 78	0 11	100
7	1 70	1 75	1 78	1 80	1 76	1 73	1 74	1 69	1 8	1 79	1 74	1 70	0 11	99
8	1 82	1 78	1 77	1 73	1 75	1 71	1 70	1 71	1 82	1 74	1 70	1 55	0 11	100
9	1 77	1 74	1 80	1 79	1 71	1 70	1 71	1 69	1 83	1 75	1 81	1 79	0 12	97
10	1 85	1 83	1 77	1 79	1 78	1 72	1 66	1 64	1 83	1 80	1 74	1 74	0 11	101
11	1 87	1 82	1 83	1 84	1 8	1 78	1 80	1 73	1 83	1 80	1 75	1 77	0 11	10?
12	1 75	1 72	1 70	1 61	1 80	1 71	1 69	1 69	1 84	1 78	1 70	1 70	0 12	95
13	1 84	1 77	1 79	1 78	1 78	1 73	1 72	1 66	1 85	1 81	1 76	1 71	0 11	100
14	1 84	1 76	1 73	1 74	1 79	1 74	1 70	1 60	1 86	1 80	1 77	1 75	0 11	99
15	1 93	1 88	1 79	1 84	1 88	1 80	1 79	1 77	1 89	1 85	1 89	1 77	0 11	10?
16	1 97	1 96	1 94	1 95	1 85	1 82	1 78	1 78	1 92	1 87	1 84	1 83	0 12	102
17	1 99	1 97	1 93	1 87	1 93	1 89	1 89	1 84	1 93	1 88	1 85	1 83	0 1?	103
18	1 93	1 69	1 86	1 86	1 85	1 83	1 86	1 83	1 94	1 88	1 84	1 83	0 1?	100
19	1 97	1 95	1 90	1 90	1 84	1 82	1 81	1 79	1 95	1 84	1 78	1 78	0 12	101
20	1 9?	1 69	1 85	1 88	01	1 95	1 94	1 90	1 95	1 88	1 91	1 90	0 12	99
21	2 01	1 95	1 90	1 87	1 90	1 98	1 85	1 83	1 95	1 91	1 83	1 84	0 12	103
22	1 89	1 89	1 86	1 83	1 84	1 83	1 83	1 83	1 95	1 86	1 85	1 8_	0 1?	97
23	1 96	1 93	1 97	1 93	1 87	1 84	1 93	1 91	1 96	1 9?	1 87	1 87	0 12	100
24	2 0	2 0	2 04	2 03	1 95	1 95	1 94	1 91	2 00	1 93	1 90	1 89	0 1	101

*) measured at three temperatures (10 20 and 37 C) with two capillaries of 0 65 mm and 0 51 mm diameters with positive pressures of 100 mmHg and 50 mmHg

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Supplementum 460

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and

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h) *For the Programs in Dalmatia and Slavonia* — Grants to Ratko Buzina from the U S Public Health Service (No HE-04774) and from the Institute of Public Health of Croatia
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EPIDEMIOLOGICAL STUDIES RELATED TO CORONARY HEART DISEASE CHARACTERISTICS OF MEN AGED 40—59 IN SEVEN COUNTRIES*

Ancel Keys (Minneapolis)

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ITALY (Rural Samples) — Flaminio Fidanza (Naples) and Vittorio Puddu (Rome)
ITALY (Rome Railroad Employees) — H L Taylor (Minneapolis) Mario Monti and Vittorio Puddu (Rome)
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YUGOSLAVIA — Ratko Buzina (Zagreb) and B S Djordjevic (Belgrade)
CENTRAL COORDINATION — Ancel Keys and Henry W Blackburn (Minneapolis)

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FOREWORD

The data presented and discussed in the following pages are the result of truly cooperative efforts actually a series of inter-connected collaborations on an international scale In effect what is presented here is a progress report on a long-time study of the epidemiology of coronary heart disease

The persons primarily responsible for the establishment of the samples and the field work in the various areas are identified as authors of Sections C1 through C9 Dr Henry Blackburn wrote Section G The senior editor wrote Sections A B D E F and H after much consultation with the persons listed on the title page who also checked preliminary drafts of these sections

Mr R Willis Parlin had a major responsibility in preparing and checking the tables and graphs as well as in the assembly of the materials for the printers Dr Martti J Karvonen shepherded the whole work through the printers

A K

GENERAL ACKNOWLEDGMENTS

Surveys of the kind reported here necessarily depend upon many people Persons who were particularly helpful in each of the areas surveyed are named *in the separate reports on those areas* Here it is fitting to acknowledge the splendid cooperation in every sample and in every area of the men who responded *to our invitation to participate Though few among the thousands of men who were examined could have had more than a vague idea of our purposes they were almost unfailingly patient friendly and anxious to help it* was a pleasure to work with them

All of us are grateful to Dr Paul Dudley *White whose continued active* interest and help in this program began with our first explorations with an international team in Naples in the *spring of 1954 His visits to the field* operations were always stimulating and his name opened many doors

Serum samples from all areas were analyzed for cholesterol in the coordinating center at the University of Minnesota This work engaged many persons but special thanks are due to Dr Joseph T Anderson who directed the analytical laboratory and to Mrs Nedra Foster who supervised the technicians Many samples were also analyzed at the Istituto di Fisiologia Umana of the University of Naples under the supervision of Prof Flaminio Fidanza

In order to assure maximum comparability in the classification of the electrocardiograms all of the tracings were independently read by at least two internists with special experience in electrocardiography Besides taking part in all of these readings Dr Henry Blackburn supervised the readings by the collaborating physicians and reconciled disagreements *in the classification Those who worked at the international level in the electrocardiographic classi*fication were *Drs* Gunnar Blomqvist (Stockholm) Ivan Mohaček (Zagreb) Raimondo Katigbak (Manila) Sven Punsar (Helsinki) and Pentti Rautaharju *(Halifax)*

Dr Josef Brozek (now at Lehigh University Bethlehem Pennsylvania) *did important* work in developing and standardizing the anthropometric methods and had a major responsibility for the measurements in the field on U S railroad employees and in Dalmatia and Slavonia

Dr J K Kihlberg R Willis Parlin and Norris Schulz of the University of Minnesota were responsible for the statistical work on the data from all of the areas in this cooperative program Ernest *Klepetar now at Columbus* Ohio provided advice

disease the limitations of such vital statistics point to the need for large-scale detailed epidemiological studies in contrasting populations on the frequency of the disease and on variables that may be involved in its etiology

Table A1 summarizes 1959 death rates ascribed to various causes among men aged 40—59 in the countries concerned in the present studies These official vital statistics indicate great differences in the reported mortality from coronary heart disease the highest (Finland and the U S A) being of the order of six to eight times the lowest rates (Greece Japan and Yugoslavia) Smaller but still very large differences are reported for deaths from all circulatory diseases Finally death rates from the sum of all causes are highest in those countries (Finland and the U S A) reporting the highest mortality from coronary heart disease suggesting a true great excess of that disease in those countries

The data of Table A1 for mortality from diseases of the circulatory system are expressed in Table A2 as percentage of mortality from all causes excluding infectious diseases and violence These latter causes are ascertained with relatively high reliability and would seem to have little or no etiological relationship to coronary heart disease On the other hand though the broad category of circulatory diseases may be relatively comparable among countries there is more question about sub-categories Cases of sudden death that would be labelled "coronary" in some countries (e g U S A and Finland) may be certified as "cerebrovascular" in some other countries (e g Japan) It is probable also that in some countries "other heart disease" includes many deaths that might more properly be attributed to coronary heart disease in contrast to the situation in the United States where there is probably a tendency to attach the "coronary" label on inadequate grounds But no matter what efforts are made to allow for these considerations and to minimize the contrasts indicated in vital statistics great differences still persist among the countries in regard to coronary heart disease or the sum of coronary plus other heart disease plus hypertension

Though Tables A1 and A2 raise important and intriguing questions it is obvious that it does not suffice to analyse vital statistics and similar official records gathered for purposes other than the investigation of the etiology of the disease As Dawber and Kannel (1963) point out such macro epidemiological materials would have limited value even if the data from different regions were strictly comparable Systematic studies are needed on contrasting populations using rigidly standardized methods and criteria so as to characterize them more precisely not only in respect to the frequency of the disease but also in respect to the distribution of variables that may be associated with the development of the disease (Keys and White 1956 Study Group 1957 Keys 1958 Research Committee 1959 Morris 1961 1962) For if there are differences in the incidence of the disease comparisons of populations in respect to associated characteristics are essential in an effort to explain the differences

Among characteristics suggested to be contributory to the development of coronary heart disease importance is frequently attributed to overweight or obesity elevated blood pressure high concentration of cholesterol in the blood lack of physical exercise and the habit of cigarette smoking The present series of papers is concerned with these characteristics and with electrocardiographic findings among middle-aged men in populations reputed to vary widely in the frequency of the disease from very high (the United

A PURPOSES, ORGANIZATION, GENERAL CONSIDERATIONS

1 Introduction

The purpose of the present communication is to report data and their analysis on some variables presumed to be relevant to the epidemiology of coronary heart disease These variables are anthropometric characteristics (including relative body weight and fatness) blood pressure serum cholesterol concentration electrocardiographic items and smoking habits as recorded for middle-aged men

The materials comprise data obtained from 1957 through 1962 on more than 12 000 men by 9 collaborating teams of investigators centrally coordinated Comparability was assured by the use of identical methods exchange of professional personnel among the teams and centralized chemical and data analysis The data are from 17 samples of men aged 40 through 59 in the U S A Japan Yugoslavia Finland Italy the Netherlands and Greece and one sample of men aged 45—64 in Italy Thirteen of these samples represent all men of given age in geographically defined areas 5 of the samples represent railroad employees

Subsequent status in regard to health and other variables is being followed in all these men Results from the follow-up will be presented in later reports The present report concerns only the findings in the cross-section surveys for the variables noted above other variables and clinical interpretations will be covered in separate reports

Publication and ascription of "authorship' of the results from the efforts of so many collaborators present difficult practical problems The present title page lists the "responsible investigators" or heads of the investigative teams who were concerned with the variables covered here The principal collaborators and professional assistants are listed in the appropriate sections of this report All of these persons share credit for the work reported here

Dietary surveys were an important integral part of these epidemiological studies but the data are not reported here the persons responsible for the dietary work will be identified in separate publications on the dietary findings

2 Coronary Heart Disease

Coronary heart disease is the leading cause of death in many of the economically more advanced and prosperous regions of the world but the incidence differs greatly among populations Such data as in Table A1 present implications for the public health and for the understanding of the etiology of this

TABLE A2

Per cent of all deaths other than those ascribed to infections and parasitic disease (B1 17) or to violence (B47 50) accounted for by deaths ascribed to all circulatory diseases to cerebrovascular disease (B22) to coronary heart disease (B26) and to all other heart disease and hypertension (B27 29)

COUNTRY	MEN AGED 40 44				MEN AGED 45 49			
	ALL CIRCUL	B22	B26	B27 29	ALL CIRCUL	B22	B26	B27-29
Finland	55	8	36	7	56	9	39	4
Greece	20	5	5	8	26	7	9	9
Italy	34	6	19	4	35	7	20	5
Japan	34	20	10	3	39	25	9	3
Netherlands	33	4	23	2	36	4	26	3
U S A White	53	4	40	4	59	5	45	4
Yugoslavia	27	7	7	10	28	7	8	11
	MEN AGED 50 54				MEN AGED 55 59			
Finland	56	8	41	4	54	9	38	5
Greece	29	9	9	9	30	8	10	10
Italy	36	9	20	5	40	11	21	6
Japan	44	30	9	4	47	34	8	4
Netherlands	35	3	26	3	38	6	27	3
U S A White	60	6	46	4	61	6	46	5
Yugoslavia	29	8	7	13	31	8	9	14

TABLE A1

Death rates per 100 000 men in 1959 from W H O Annual Epidemiological and Vital Statistics Geneva 1962 classified according to the Intermediate (A) and Abbreviated (B) lists in the Manual of the International Statistical Classification of Diseases Injuries and Causes of Death (1957 Geneva) "Infection" comprises B1-17 "All Violence " B45-50 "All Circulatory " B22 B24-29 A85 86 "Cerebrovascular " B22 "Coronary " B26 "Other Heart " B27 "Hypertension " B28-29

CAUSE	FINLAND	GREECE	ITALY	JAPAN	NETHER-LANDS	U S A WHITE	YUGO SLAVIA
MEN AGED 40-44							
All Causes	500 0	260 0	330 0	420 0	240 0	420 0	378 1
Infection	55 4	32 3	39 5	71 6	9 8	8 3	78 1
Violence	118 4	46 7	66 4	88 9	44 3	92 2	97 0
All Circulatory	178 9	36 7	77 1	88 7	62 1	170 6	54 2
Cerebrovascular	26 4	9 6	12 7	51 2	7 1	14 2	13 6
Coronary	117 5	8 7	42 1	24 7	42 7	126 8	13 6
Other Heart	11 1	12 2	5 5	4 5	2 8	6 2	21 9
Hypertension	10 2	2 1	3 8	4 3	1 5	6 1	-
MEN AGED 45-49							
All Causes	780 0	450 0	520 0	640 0	390 0	690 0	577 7
Infection	64 9	48 8	49 2	93 4	11 5	13 1	111 7
Violence	144 3	60 3	75 6	102 5	44 5	103 1	93 8
All Circulatory	317 6	90 0	139 9	174 1	120 2	338 3	106 0
Cerebrovascular	51 9	24 6	28 8	112 2	14 0	27 4	25 1
Coronary	223 7	30 1	78 4	41 3	85 3	259 2	30 5
Other Heart	14 5	25 5	10 6	6 8	7 5	11 5	40 3
Hypertension	9 1	4 7	7 7	8 5	4 1	14 3	2 1
MEN AGED 50-54							
All Causes	1290 0	650 0	890 0	1020 0	690 0	1150 0	984 3
Infection	109 0	55 7	73 7	115 6	14 3	21 0	165 4
Violence	159 7	51 6	94 6	111 9	58 0	115 8	113 9
All Circulatory	569 9	157 6	260 3	352 4	218 7	608 5	201 9
Cerebrovascular	85 7	48 0	63 7	240 7	21 0	56 7	54 7
Coronary	422 6	48 0	145 5	70 9	162 1	465 8	51 1
Other Heart	24 1	44 8	17 9	14 1	12 0	17 5	81 8
Hypertension	19 9	5 4	15 9	16 2	7 0	27 4	7 1
MEN AGED 55-59							
All Causes	2030 0	1120 0	1460 0	1680 0	1210 0	1790 0	1637 5
Infection	151 5	68 7	87 3	149 3	17 9	32 1	233 4
Violence	171 2	63 2	97 1	133 2	82 4	125 4	133 4
All Circulatory	926 3	291 7	509 3	659 8	423 3	988 0	397 [illegible]
Cerebrovascular	159 8	83 4	144 3	468 4	63 1	102 4	100 5
Coronary	643 2	95 4	270 1	114 9	297 5	748 2	112 0
Other Heart	56 0	85 1	35 1	28 9	21 7	26 3	158 8
Hypertension	31 1	14 2	36 0	31 5	11 1	49 6	13 5

is of the order of 30 per cent (Biörck *et al* 1960)

Data from cross sectional surveys depict characteristics of the population at the time and allow comparison to be made between healthy" persons and certain kinds of patients with coronary heart disease In estimating prevalence the greatest security is with the select group of survivors of myocardial infarction who happen to show persisting electrocardiographic evidence of previous infarction or for whom convincing old records can be found to prove that infarction occurred at some time in the past To these may be added individuals who are judged to have classical angina pectoris though if the criteria are rigidly specified the number of doubtful cases will outnumber those who unquestionably merit the diagnosis Finally there are persons in the greay area" those with non specific electro cardiographic abnormalities — flat or depressed ST segments and T waves the various disturbances of rhythm

Obviously unless great conservatism is exercised false diagnosis will be frequent But if conservative diagnosis is adhered to missed diagnosis will be at least equally frequent Finally whatever criteria are used the prevalence survey will result in a group of patients about whom we must ask whether some of their other characteristics may not be results of the clinical disease and not representative of them in the pre disease situation

Some of these difficulties in cross-section surveys can be avoided and others reduced in prospective studies which start with the study of persons initially healthy who are followed until enough of them have developed the disease to allow comparison with the persons in the cohort who remain healthy Longitudinal studies of this type require much more time and effort but are correspondingly more significant

5 Current Epidemiological Studies in the US

The incidence of coronary heart disease among middle-aged men is such that in many populations a few thousand subject years follow up will provide an adequate number of cases for statistical analysis Such a study was started in Minnesota in 1947 (Keys *et al* 1963) and others began later at Framingham (Dawber *et al* 1957 Dawber and Kannel 1961) at Albany (Doyle *et al* 1957 1959) at Los Angeles (Chapman *et al* 1957) at Chicago (Paul *et al* 1963) and elsewhere in the United States

Important findings are emerging from these follow-up programs in he United States It is gratifying to note the consistency in the results but this also points to several limitations In the first place all these studies concern men in one particular culture that of contemporary urban United States and some of the associations among variables that emerge may not be universal to other cultures socio-economic patterns and regions In the second place the samples are by no means random they were selected by employment or availability except in the case of the Framingham study In the latter though a random roster of the small town of Framingham was used for eligibility to enter the study about a third of the men eligible did not come into the study they selected themselves out of it (Dawber *et al* 1957) Finally these American population samples are characterized by a relatively high degree of homogeneity in certain respects of mode of life so that they throw little light on the effect of differences in mode of life The incidence rates of coronary heart disease are so similar in all of these studies that there is little basis of contrast on which to compare the several samples Physical activity and diet

States and Finland) to low incidence (Japan and countries of the Eastern Mediterranean)

3 The Epidemiological Approach

Epidemiological investigations alone seldom if ever yield final proof of causation but they offer a powerful tool to discover associations among variables to provide clues for further investigations to test hypotheses of cause and effect and to indicate practicalities to consider for possible programs of prevention and control (Keys 1957)

The utility and even the necessity of the epidemiological approach as a major but not exclusive method in the effort to develop methods to control coronary heart disease is emphasized by the limitations of clinical and experimental approaches

Serious questions arise about the relevance of data from experiments on animals to the actual interplay of causal influences in the etiology of the disease in man These questions concern the progression from atherosclerosis to infarction as well as the development of the primary atherosclerosis The basic arterial disease may be mimicked in some experiments on animals — though exact correspondence is debatable — and details of pathogenetic mechanisms may be studied in this way But the quantitative equivalents of the variables that promote pathogenesis in man cannot be specified for other species The etiology of the disease in man concerns quantitative influences that operate over many years these must be evaluated in man himself

As to the clinical approach it may be suggested that often it is only epidemiology applied to inadequate numbers in any case it has serious limitations The causative influences of the basic disorder begin to operate long before coronary heart disease is clinically recognizable and may even have disappeared before that time Furthermore in populations beset with this disease in epidemic proportions comparison of patients with so-called controls is complicated by the fact that many of the controls themselves are afflicted with severe but as yet silent coronary atherosclerosis and any analysis is necessarily probabilistic (White et al 1950 Larsen 1954 Keys and White 1956 Larsen and Bortz 1960) Finally the high early mortality in the first heart attack means that clinical studies generally cover only certain kinds of coronary patients those who survive long enough to be studied

The ultimate clinical event of myocardial infarction or acute coronary thrombosis is a distinct entity but angina pectoris is by no means so sharply defined and the underlying arterial disease shows no clear demarcation in the transition from the "normal clean" artery to the situation that is grossly pathological There is reason to believe that causative influences too operate quantitatively and in an additive fashion It is obvious then that the relevant variables should be measured and analyzed quantitatively and with due regard to interrelationships among variables

4 Cross-Section versus Follow-up Studies

Cross-section surveys on coronary heart disease may reveal prevalence but they do not indicate incidence or the sequence of events and they tell us nothing about the characteristics of persons who die suddenly The importance of this latter fact in the case of coronary heart disease is apparent when it is realized that the acute mortality (first 30 days) of the first heart attack

limited partly because of limited funds partly because suitable methods have not yet been developed for epidemiological application

However from the initial cross-section surveys the numbers are adequate to indicate in some detail distributions and interrelationships of the measured variables and to make some population comparisons Attention to the avoidance of bias in sampling has avoided some common faults in population studies but questions remain The "chunk samples dealt with in Europe and Japan though unbiassed in respect to the particular areas selected for study are not claimed to be necessarily good samples of the whole region in which they reside let alone of the countries The U S railroad employees studied are not claimed to be an ideal sample of all U S railroad employees there were too many men in the samples who refused to cooperate And the Roman sample may be unrepresentative of railroad employees in Italy as a whole But we should not deprecate too much the samples are better than those previously studied Besides a good theoretical argument can be made that no sample can perfectly represent a population unless it corresponds in all particulars of the distributions of all relevant variables in that population since this fact can never be guaranteed in any real situation no sample can be perfect

9 Features of the Cooperative Program

The basic plan of the program from which data are reported here was to organize *parallel* studies on men aged 40—59 in areas differing in the diet or in the reputed incidence of heart disease or both but with areas so chosen that within each area there would be relative homogeneity In Europe rural areas dominated by simple agricultural pursuits were selected in which virtually all men of given age would be covered an optimistic plan justified as shown in Section 12 below by previous explorations In Japan the farming and fishing village areas of Tanushimaru and Ushibuka were similarly covered by such chunk' samples A departure from the concentration on rural populations is the study of the men of Zutphen a small town in central Holland in which unlike the rural areas most of the men are not farmers but are engaged in trade and light industry

In the United States it was not feasible to organize a program with rural populations that would be reasonably comparable to the European populations However a parallel pro gram was organized to study several occupational categories of men aged 40—59 employed by railroads operating in the northwest sector of the country The sampling procedure used in this study will be described in detail in the specific section of this report covering U S railroad employees Three major occupational categories of the railroad employees in the U S A were distinguished clerks yard switchmen and executives the switchmen are physically moderately active while the men in the other two categories are sedentary More careful scrutiny showed that certain types of U S railroad "clerks" are not sedentary in their occupation eventually the clerks were distributed into sedentary and non-sedentary clerk categories

The sample of railroad employees in Rome comprised four categories station masters and dispatchers (sedentary) switchmen (rather comparable to the U S switchmen) maintenance-of way workers (heavy work) electrical maintenance workers (generally active but variable in level of activity)

A major feature of the entire program was the adoption of rigidly

too, do not show great contrasts among the samples and even within the samples variability in *these items is* restricted

The association among variables which seem to be most important in the etiology of this disease in one population may not apply or may be overshadowed by other factors in other populations Universals in the disease will be clear only when populations of differing habits and cultures are included in broader studies

6 Epidemiology in Contrasting Populations

Epidemiological studies comparing populations affording great contrasts especially in regard to the diet and the reputed frequency of ischemic heart disease have provided useful data in cross-section surveys of contrasting socio-economic groups in Madrid (Keys *et al* 1954a) Naples (Keys *et al* 1955) Guatemala City (Scrimshaw *et al* 1957) and of different racial groups in Cape Town (Bronte-Stewart *et al*, 1955) But complicating and perhaps confounding variables are introduced when comparisons are made among differing socio-economic classes *especially when the lower end of* the scale is represented by a population seriously underprivileged in many respects *including medical services* and food The addition of the variable of race involving great differences in *mortality* in youth and in exposure to infectious and parasitic disease further complicates the picture

7 An Ideal Epidemiological Program

Consideration of the points made in the foregoing sections tends to define the character of ideal epidemiological studies concerned with the universals of this disease They should begin *with detailed* measurements and examinations of samples of persons in contrasting populations and should cover a *number of variables that are of potent*ial relevance to the etiology of or susceptibility to the disease Careful follow-up will *then reveal incidence* and will relate the development of the disease to pre-disease characteristics Because comparisons are so vital in such studies we reiterate the point noted previously — rigidly standardized methods and criteria must be applied

The practicalities to meet these requirements are formidable and could scarcely be met by any single investigative unit let alone any single investigator But it proved to be feasible to organize a group of investigative teams in different countries who would agree on indentical protocol methods criteria *and analytical treatment and to make* arrangements to maintain comparability by exchange of professional personnel and centralization of analytical work

8 The Present Report

The present report concerns data from the first phase the cross-section *survey of an attempt at such a broad* cooperative epidemiological study involving parallel studies on many samples of men by independent but coordinated teams in a number of countries It will be evident that though the *program was ambitiously conceived* and has operated well within the limits originally set it is far from a close approach to the ideal The subjects comprise 12 293 men yet the number is too small to allow more than limited conclusions about coronary heart disease itself unless as hoped the follow-up extends to 10 or more years The number of variables studied is also

limited partly because of limited funds partly because suitable methods have not yet been developed for epidemiological application

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A major feature of the entire program was the adoption of rigidly

standardized methods and criteria a common protocol and battery of observations and tests and central coordination to assure so far as possible complete comparability of the data collected Further to assure such comparability arrangements were made for interchange of professional personnel among the teams working in the several areas and for centralization of statistical and some analytical services It was not possible to arrange such interchange for Japan but Prof Kimura worked with the other teams in Minnesota Greece and Italy and Prof Keys participated with Prof Kimura's group in an earlier exploratory survey in Japan (Keys *et al* 1958 a)

Accordingly the idea of "chunk sampling" of a defined geographical area was tried out in 1957 with studies on men aged 45—64 at the large village of Nicotera (Calabria), Italy, and in a series of villages in the central part of the Island of Crete Greece The experience in 1957 showed the feasibility of obtaining nearly complete coverage of such designated samples in villages by detailed examinations and emphasized the value of using international teams in these programs The professional staff working together at Nicotera and Crete represented nine countries (England Finland France Greece Italy Japan the Netherlands U S A and Yugoslavia)

10 Preceding Experience in Field Work

The studies from which data are reported here were preceded by extensive experience in field explorations directed towards the question of the epidemiology of coronary heart disease and possible relationships with predisease characteristics and mode of life including the diet and physical activity This work began in 1952 in Italy Spain and England and later extended to South Africa Japan and Finland (Keys 1952 1953 Keys *et al* 1954 a 1954 b Keys and Keys 1954, Bronte-Stewart *et al* 1955 Keys *et al* 1955 1956 Brozek *et al* 1957 Keys *et al* 1958 a 1958 b Karvonen *et al* 1959) Explorations with U S railroad employees began in 1956 and a start on systematic larger scale studies was made in 1957 (cf Taylor *et al* 1962)

These studies disclosed significant contrasts especially in regard to serum cholesterol and the diet and pointed to the need for larger and more systematic operations with careful attention to sampling and uniform protocol

11 Organization of Programs Providing the Present Data

The extensive explorations prior to 1957 led to more systematic programs with a plan to follow-up the men examined for 5 or more years It was agreed that a suitable age range would be 40—59 and that a series of population samples should be studied in parallel Accordingly new programs from which data are here reported were started in 1957 with the railroad employees in the U S A and in 1958 in Dalmatia and Slavonia Yugoslavia and were followed by the programs which began in two areas of Finland in 1959 and in 1960 at Crevalcore and at Montegiorgio in Italy at Zutphen the Netherlands and again on Crete In 1961 the sample on Corfu Greece was examined In 1962 another study was added at the village of Velika Krsna 50 km south of Belgrade Yugoslavia and the sample of railroad employees was examined in the same summer The program in Japan not strictly comparable in all details began in 1958 at the farming village of Tanushi-

maru and in 1960 at the fishing village of Ushibuka The present publication reports initial examination findings in all these areas

Members of the Central Organization (Prof Keys and Dr Blackburn) work closely with teams in each of the countries During the period of the initial examinations in each area the Central Organization provided help to the local organizations in the form of supplies equipment and professional personnel

Financial support is indicated on the front page of the report Many persons and organizations aided the work and so far as space permits these are indicated in the appropriate separate sections below

12. Establishment of Rosters

The starting point in any program that aims to cover properly defined samples is to establish a true roster of all persons of the designated age and sex in the area under study The procedure developed at Nicotera and on Crete in 1957 was later applied to the other areas in Europe and so may be described here

In the areas of work in Europe and Japan official lists of residents with birth dates are locally available However such lists require careful scrutiny Men who migrate away from the area are often long retained on the list of residents while newcomers particularly from the same general region may no be listed for years And inevitably there are clerical errors in names and dates and delays in correcting for deaths Parish church registers electoral and taxation lists provide additional data but detailed local enquiry among responsible residents is essential As examples Table A3 summarizes the roster development and eventual examination coverage in the studies in 1957 at Nicotera and on Crete

At Nicotera it was found that many residents' had long since moved to other parts of Italy or had emigrated abroad 2 men had simply not been seen or heard from for many years and 9 men recently dead were still listed as residents In contrast to the reduction of 81 men by net corrections at Nicotera in the villages of Crete the rolls failed to list many men who years previously had moved to these villages from nearby so there was a net correction of +31 men

In such rural areas it is possible to obtain remarkable cooperation with very few refusals of examination At Nicotera and on Crete in 1957 such refusals amounted respectively to only 2 1 and 1 7 per cent of the men

This method of establishing rosters was applied to all samples except the railroad employees Wage rolls and employment records were used to develop the lists of men aged 40 through 59 in the selected occupations in the railroad samples

Ages indicated in the rosters were checked against birth dates as personally stated and on identity papers in cases of possible doubt these were further checked against birth registries in churches and elsewhere The *men* studied were 40 through 59 years old (attained age) at the time of examination except *in the Nicotera sample* in which the age range was 45—65

13 Sample Coverage

Twelve of the samples concerned the total population of men of specified ages resident *in* the defined rural geographical areas By "resident" was meant men who regularly resided in the area even though they might be temporarily absent at the time of the examinations A few men were excluded

TABLE A3

Development of sample rosters and eventual coverage in examinations of men aged 45 65 in 1957 in Nicotera Italy and in 12 villages near Heraklion Crete Greece

ITEM	NICOTERA	CRETE
Initial "official" resident rolls	703	631
Corrections		
Emigrated or long settled elsewhere	-81	-22
Additions from incomplete registry etc	0	+53
True roster eligible sample	622	662
Not examined		
Pulmonary t b in hospital	3	2
Disabling illness verified not cardiovascular	8	1
Not in area reputed "healthy"	0	3
Refused apparently healthy	12	11
Refused possible heart disease	1	0
Total not examined	24	17
Total examined	598	645
Sum	622	662

who coming from more than a few kilo meters away had moved into the sample areas only in recent years A few other "newcomers" originally from nearby villages of the same type were accepted into the samples

In one area (Zutphen the Netherlands) the total population of men aged 40—59 was too large to be covered by the resources of the team For that area after establishing the roster 5/9ths of the names were drawn at random by an independent statistician and the resulting 1088 men constituted the eligible roster

Accordingly there were 13 "chunk" samples of all men of specified age in the defined areas Among the total of 9564 eligible men 9170 were examined in full the coverage being 95 9 per cent Details are given in Table A4

Five samples of railroad employees were studied as shown in Table A4 In addition some railroad employees in other occupations as well as volunteers were studied data on these men are not included in the present report which concerns 2908 railroad employees who represented about 70 per cent of the eligible men For all 18 samples the data on the 12 078 men reported here cover 87 9 per cent of all men eligible

It is notable that the coverage was nearly perfect in the rural areas less satisfactory in the small town of Zutphen and considerably poorer among the railroad employees The latter result in the U S A was not attributable to lack of opportunity for the men to be examined or of effort in recruitment as will be seen in the separate section below dealing with the U S railroad employees

Most of the men missed in all of the samples represented refusals on emotional grounds — dislike of doctors or examination procedures — especially venipuncture apprehension that some "catch" was involved or general perversity In the chunk" samples many of the men missed were temporarily absent from the area at the time of examinations some of these men were examined later but their data are not included in the present analysis Very few men failed to be examined because of illness Among the U.S railroad employees information from other sources indicated that few of the refusals were related to the state of health though in some cases fear of possible discovery of illness that might affect employment was a factor — in spite of repeated assurances that all findings were completely confidential

14 Examination Procedure

The methods used in the examinations are described in detail in Section B METHODS below which also gives data on reproducibility

Great efforts were made to assure comparability of methods and procedure in the several areas Except at Zutphen and in the two areas in Japan the locally responsible team was aided in the field by professional experts from the teams in other countries Electrocardiograms were independently classified by two or more electrocardiographers at least one of whom was from another country

The general procedure for the examinations in the field developed at Nicotera and Crete in 1957 was applied thereafter in the programs elsewhere After the roster was established a schedule of examinations was adopted and headquarters were organized both for the examination and for housing the team of investigators and assistants For the U.S railroad men specially fitted railroad cars were used for the examinations For the Roman railroad men examination rooms were provided at the central railroad station (Stazione Termini) in Rome For the other areas

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ITEM	NICOTERA	CRETE
Initial "official" resident ro'ls	703	631
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Not examined		
Pulmonary t b in hospital	3	2
Disabling illness verified not cardiovascular	8	1
Not in area reputed "healthy"	0	3
Refused apparently healthy	12	11
Refused possible heart disease	1	0
Total not examined	24	17
Total examined	598	645
Sum	622	662

examination sites were located in schools farm houses etc

In each area local assistants made appointments with the subjects and then reminded or escorted them on the appointed day so as to assure attendance at the examination centers Transportation was provided when needed Efforts were made to prevent the men from indulging in heavy exercise or a heavy meal beforehand While waiting smoking was not allowed When called in the procedure was as follows

a *Registration* — assignment of serial number record name address father s name age and birth date (giving a check on age) marital status and other family data present and past occupation habitual physical *activity* smoking habit

b *Anthropometry* — disrobe record height (without shoes) weight (in underclothes) sitting height bi acromial and bi cristal diameters arm and scapula skinfold thicknesses

c *Medical* — medical history physical examination record supine blood pressure twice take venous blood sample

d *ECG* — record 12 lead ECG in rest and again immediately after a 3 minute exercise test (step test)

e *Urine* — urine sample qualitatively tested for sugar and albumin

f *Respiration* — record vital capacity and timed forced expiration (This procedure was introduced with U S railroad workers in 1958 and in Finland in 1959 It was not used at Zutphen or in Japan)

g *Dismissal* — after brief remarks by physician

15 Forms and Codes

Comparability of data convenience in recording and subsequent statistical analysis are greatly aided or even require suitable standard forms and codes Such forms and codes developed for common use in these collaborative studies cover medical history the physical examination parental mortality family status smoking habits *anthropometry* etc but for the present purpose it is not necessary to refer to all of these

The OCCUPATION CODE is given in the Appendix This code is intended to identify the general character of the occupation and to suggest the probable socio economic status of the man as indicated by occupation It is not intended to indentify all specific occupations but it distinguishes 98 categories (thereby requiring only two columns of a punch card) into which most men are readily classified the remaining men can be fitted in without serious distortion for the purpose of this code For some purposes it is useful to compare the professional and management occupations with craftsmen or clerical workers without regard to the particular professions or crafts or clerical jobs concerned The Occupation Code allows this to be done readily

The ELECTROCARDIOGRAPHIC CODE is given in detail in the Appendix The "Minnesota Code" (Blackburn *et al* 1960) is intended to give an objective picture of the electrocardiogram without insisting on any particular interpretation though the items classified are those commonly accepted as being important for interpretation The revision of the original published S T depression coding should be noted in the version of the Appendix

The SMOKING CODE given in the Appendix classifies men into more categories than are necessary or useful for the present purpose As will be seen in Section F SMOKING below various categories were combined in a simpler classification in the actual analysis of the data

TABLE A4

Examination coverage "Roster" gives the true total number of all eligible men "No Examined" does not include a few men examined at a later date

AREA OR GROUP	DATE	ROSTER No Men	EXAMINED No Men	%
Nicotera, Italy	Fall, 1957	626	607	97 0
Switchmen, U S A	1957-1959	1414	835	59 1
Sedentary Clerks, U S A	1957-1959	1163	861	74 0
Non-Sedentary Clerks, U S A	1957-1959	233	155	66 5
Executives, U S A	1957-1959	363	251	69 1
Tanushimaru, Japan	Spring, 1958	509	509	100 0
Dalmatia Yugoslavia	Fall, 1958	742	727	98 0
Slavonia, Yugoslavia	Fall, 1958	815	749	91 9
East Finland	Fall, 1959	823	817	99 3
West Finland	Fall, 1959	887	860	97 0
Crevalcore, Italy	Spring, 1960	1012	994	98 5
Montegiorgio, Italy	Spring, 1960	727	719	99 0
Zutphen Netherlands	Summer, 1960	1088	917	84 3
Ushibuka Japan	Summer, 1960	506	504	99 6
Crete, Greece	Fall, 1960	703	686	97 6
Corfu, Greece	Fall, 1961	555	529	95 3
Railwaymen, Rome, Italy	Summer, 1962	(1000)*	806	(80 6)
Velika Krsna, Yugoslavia	Fall 1962	571	552	96 7
Total All groups		13737	12078	87 9

*A total of 1241 men were eligible from the roster but because of known conflicts in schedule, only about 1000 were actually invited

is developed from the start on a warm and personally sympathetic basis The subject may seem to be only a serial number on the roster and appointment schedule but he must never be treated that way Ideally a brief note about the findings on each man is provided to the local physician or public health nurse *not* to the subject himself When it is not feasible each subject should be given a few words of reassurance at the end of the examination When medical care is really needed efforts must be made to provide this through local sources

The experience of the teams in the field in Europe and Japan quickly made convinced internationalists of most staff members Political arguments were avoided and concentration was on the *professional* and purely individual human aspects of the work and life together the result was the development of true friendships among staff workers of all nationalities and the most cordial cooperation of the subjects their families and the local official Though the subjects frequently had little comprehension of what the work was all about the good will on both sides was readily apparent it was often a problem to escape too much local hospitality in the villages

Headquarters and laboratories for the wo k on the Roman railroad employees were established at the main railroad station of Rome The studies on U S railroad employees posed special practical problems Headquarters consisted of two specially fitted railway cars with all necessary apparatus installed in them After suitable advance preparation including meetings with the unions in each town these cars were hauled into the railroad yards or stations of each of the several locations where men were to be examined In spite of letter phone and personal solicitation many men on the roster did not appear for examination when the team visited the locations and a second round of travel to these locations was necessary to reduce the number of "no shows"

All of these efforts still resulted in less complete coverage of the rosters of railway employees than obtained in the villages abroad though the percentage response was similar to that obtained in other surveys in the U S (cf Dawber *et al* 1957) The discrepancy between responses in the U S and abroad reflects basic differences in attitudes of the populations and not in the effort or attitudes of the investigators In general the response of the populations to the appeal to participate in such surveys tends to be inversely proportional to the size of the community the response is better in villages than in towns and better in towns than in cities

16 Physical Activity

Physical activity is a variable in the mode of life that may well be an important factor in susceptibility to coronary heart disease Accordingly, the attempt was made to classify every man into one of three categories in regard to general level of habitual activity 1) sedentary, 2) moderately active 3) heavy physical activity

This is a coarse gradation but further refinement was considered to be unjustifiable without the use of much more elaborate means of ascertainment than available from a few questions and answers At the extremes of this 3-class scale might be 0) bed ridden and 4) extremely heavy activity but the few bed ridden invalids are otherwise identifiable and the line between 3) and 4) would be difficult to draw

It should be noted that the physical activity classification is not necessarily dependent on the occupational category though in many cases there is a close connection especially in this age range and in rural populations where voluntary physical activity for recreation seldom amounts to much in comparison with the occupational activity

17. *Practicalities of Field Work*

Each area has its peculiarities that affect practical details of organizing and operating cardiovascular surveys and related field work but the following notes are generally applicable to the studies reported here

It is difficult to engage first-class professional personnel to stay in the field away from their home headquarters for more than a few weeks at a time so the schedules for field work were planned accordingly Selection of the period for field work in a given area required consideration of the seasonal activity of the subjects as well as that of the proposed staff and in general this means concentration of the examinations in a period of not over one month Before the field work proper begins the final roster of subjects must be established local headquarters arranged suitable local assistants engaged and provision made for local transportation of both subjects and staff

In general it was found to be efficient to organize schedule and staff so as to "process" from 150 to 200 men per 6-day week this required making effective arrangements to have the subjects available on schedule It proved to be suitable to concentrate the examinations in the mornings (say 8 to 13 o clock) leaving the afternoons for "book work" ECG classification working up blood samples etc plus handling a few stragglers that cannot be examined in the mornings The clinicians schedule had to allow for the fact that in many areas it is impossible to avoid some demands for medical advice particularly for local women and children

Such a program for cardiovascular field surveys requires a staff as follows (asterisks denote personnel who need not be natives of the country) Director of Field Operation (one other senior professional person should be designated as his deputy) two internists to take histories and make physical examinations one electrocardiographer* one physician or physiologist to conduct respiratory tests one biochemist or chemical technologist* one anthropometrist*, one registrar (may be local) one or more clinical consultants* two assistants for ECG recording (one may be local) and about four helpers (a recorder a "man catcher" to bring in subjects and run errands a driver and a dishwasher and general helper)

Every effort should be made to assure that the relationship with the subjects

calipers were used for repeated measurements on the same men Table B1 summarizes a comparison of the "Lange" (Cambridge Scientific Industries Inc Cambridge Maryland) and "John Bull" (Harpenden British Indicators Ltd Sutton Road St Albans Herts England and H E Morse C 455 Douglas Ave Holland Michigan) calipers which have become the standard instruments in our skinfold measurements With these particular samples of calipers the Lange tended to give a slightly smaller reading than the John Bull caliper but the mean difference of 0 233 mm for the 10-second reading is entirely trivial Even when the reading is delayed until the skinfold has been under pressure of the caliper spring for 60 seconds the discrepancy between the two calipers though larger (mean $\Delta = 0.407$ mm) is negligible

The skinfold deforms under the pressure of the caliper so that the reading becomes smaller as the time extends from a quick reading at 5—10 seconds to a slow reading at 60 seconds Table B2 shows this effect and the fact that the deformation increases with increasing thickness of the skinfold This produces no significant error except in very fat or edematous persons but the effort is made to avoid the effect by reading rapidly

The Sitting Height was measured to the nearest mm with the subjects seated in erect position on a firm stool with a horizontal surface The subject s back was in contact with the wall at the regions of both scapula and buttocks The line of sight was horizontal and the manipulation involved in determining level of the top of the head was identical with that u ed in measuring s anding height

The Bi-acromial Diameter a measure of the width of the shoulder girdle was obtained as the distance between the most lateral margins of the acromial process of the scapulae as measured with a pelvimeter to the nearest mm Definite effort was made to have the subject relax the shoulders since the position of the shoulders affects importantly the apparent value of the bi-acromial diameter The aim is to obtain the maximal value of the bony diameter

The Bi-cristal Diameter a measure of the width of the pelvic girdle is defined as the greatest distance between the lateral margins of the iliac crests Systematic endeavor was made to avoid or at least to minimize the contamination of the bony measurement by the overlying soft tissues This was achieved by exercising pressure when necessary on the contact surfaces of the pelvimeter the measurement again being made to the nearest mm

Anthropometry — Derived Indices Indices of body type and configuration or shape may be derived from such items of measurement as indica ed above and are commonly expressed in relative terms in view of the lack of agreed absolute mea_ures In spite of the obvious need for such indices there is little or no agreement even about relative measures Those chosen for the present studies have the advantages of being simple objective numerical expressions of what seem to be reasonably acceptable concepts of typology though their interpretation may provoke more argument than agreement

Relative Body Weight has been expressed in so many ways that it is clear no one way is ideal or even theoretically of outstanding merit A main purpose of attemp ing to provide a measure of relative body weight is to enable individuals to be compared with the population as a whole having due regard to age and sex The most common application of such comparison is to estimate relative overweight this being assumed to be a measure of

B METHODS

1 Anthropometry

The standard examination battery included anthropometric items to be used as indices of gross body size (height and weight) of skeletal form or configuration of relative body weight, and of body fatness The recommendations of the Committee on Nutritional Anthropometry (1956), Food and Nutrition Board of the National Research Council were followed for the items of measurement to which they apply

Height Standing height (stature) was measured as the distance from the soles of the feet to the top of the head without shoes The subjects stood erect and both the heels and the scapulae were in contact with the wall to which a steel tape graduated in mm was affixed The head was held so as to make the line of sight horizontal A wooden or metal L-bar held against the tape was lowered until it made firm contact with the top of the head Stature was measured to the nearest millimeter

Body Weight was measured with the men wearing light underwear When anything but light socks and light underwear were worn a correction was made before recording the weight Such a correction was required only rarely principally in areas in which the examinations were made in the cool weather of late fall The measurements were made to the nearest 0 5 kilogram

Skinfolds indicating subcutaneous fatness and by inference relative obesity or leanness measured with calipers exerting a constant pressure of 10 g per square mm and a jaw face of 20 square mm were recorded at two sites on the upper arm and below the scapula The upper arm site is located at the dorsum of the right arm at the level midway between the tip of the acromial process and the tip of the elbow The skinfold is parallel to the long axis of the arm The "skin" is lifted and the fold is held firmly between the index finger and the thumb of the examiner s left hand placed about 1 cm above the level at which the measurement is to be made If arm circumference is measured at the same level it is advantageous to mark the level with a dermatographic pencil The scapular skinfold is measured just below the tip of the right scapula The skinfold is lifted along the line of least resistance typically forming an angle of about 45° with the spine the line going downward For most of the analyses in the present work the sum of these two skinfolds in mm was used as an index of *fatness or relative obesity*

Several makes of calipers were used but no significant differences in the results were observed when different

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Relative Body Weight has been expressed in so many ways that it is clear no one way is ideal or even theoretically of outstanding merit A main purpose of attempting to provide a measure of relative body weight is to enable individuals to be compared with the population as a whole having due regard to age and sex The most common application of such comparison is to estimate relative overweight this being assumed to be a measure of

TABLE B1

Comparison of Lange and "John Bull" (Harpenden) *skinfold calipers in duplicate* measurements on farmers aged 40-59 Lange values minus John Bull values in mm Lange calipers used first with 25 men, second with another 25 men

ITEM	READINGS AT 5-10 SECONDS		READINGS AFTER 60 SECONDS	
	Lange First, John Bull Next		Lange First, John Bull Next	
	Triceps	Scapula	Triceps	Scapula
Mean Δ	-0 236	-0 188	-0 408	-0 368
S E M	0 259	0 249	0 349	0 348
	John Bull First, Lange Next		*John Bull First, Lange Next*	
	Triceps	Scapula	Triceps	Scapula
Mean Δ	-0 404	-0 104	-0 576	-0 276
S E M.	0 371	0 277	0 474	0 350

$(S\ E\ M\ )^2 = (\Sigma\Delta^2)/2N$, where N is number of pairs of observations

TABLE B2

Change in skinfold measurement under a pressure of 10 gm per square mm Measurements on 50 farmers aged 40-59 N = number of pairs of measurements after 5-10 seconds and after 60 seconds of comparison

LOCATION	Range, mm after 5-10 secs	N	Δ after 60 seconds, mm Mean	S D	S E
Triceps	Under 4 1	24	-0 38	0 145	0 030
"	4 1 to 6 0	45	-0 49	0 216	0 032
"	6 1 to 8 0	25	-0 58	0 216	0 043
"	8 1 or More	6	-0 90	0 110	0 045
Scapula	Under 6 1	22	-0 46	0 144	0 031
"	6 1 to 8 0	46	-0 53	0 157	0 023
"	8 1 or More	32	-0 67	0 315	0 056

obesity or body fatness The assumption can lead to serious errors Extreme overweight is certainly associated with excess fat but at lesser degrees of departure from the population average the correlation is far from perfect it is possible to be overfat and not overweight or the reverse (cf Keys 1955a 1955b) Sedentary men are less muscular than men who habitually do manual labor with the result that their body weight is less than might be expected to correspond to their degree of body fatness

Besides this complication of body composition in the interpretation of relative weight there is an equally serious effect of differences in skeletal type The man with short legs and wide pectoral and pelvic girdles must necessarily be relatively heavy for his height So relative body weight is a complicated index which often has no simple interpretation

Insurance company studies on the mortality of their policy holders have long stressed relationships between relative body weight and morbidity and mortality especially from heart disease (Society of Actuaries 1959) so it seemed important to consider this variable in the present study Moreover this consideration also suggested the desirability of using the same method of estimating relative weight as used in the insurance studies

Accordingly in the present studies relative body weight was calculated as percentage of the average weight of men of given height and age as reported in the Medico-Actuarial Investigations (1912) These averages have no universal significance in the bio-medical sense being simply the averages for American men mostly in urban centers on the eastern seaboard of the United States who applied for life insurance in the general period of about 1890 to just after the turn of the century Their virtue is that they provide a single set of standards that have had wide distribution and application The basic data used in the calculation of relative body weight are given in the Appendix

Relative Height of Trunk Plus Head is useful in classifying individuals in regard to one aspect of skeletal form the length of trunk The index is simply the standing height minus the sitting height (i e trunk plus head height) expressed as a percentage of the standing height

The Laterality — Linearity Index is the ratio of the sum of the bi acromial and bi-cristal diameters to the height or total body length This is a simple measure of the general shape of the body the larger the index the greater the relative breadth or laterality of the skeleton

The Ratio of Shoulder to Pelvis Width or more precisely the ratio of the bi acromial to the bi-cristal diameter is a basic item of the skeletal form which is related to the masculinity — femininity scale *The greater this ratio the more masculine" is the skeleton*

2. Blood Pressure

Instruments used for indirect arterial blood pressure measurement were all upright mercury columns with wrap-around arm cuffs bladder size 12 x 23 cm Personal stethoscopes were employed Formal training and testing of observers was limited to explanation of the principles involved in standard measurement demonstration of technique and supervision Conditions of measurement and procedure included comfortable room temperature which caused no shivering or sweating in subjects unclothed to the waist Smoking eating and vigorous activity were avoided for a minimum of 30 minutes and usually over an hour and venipuncture usually preced-

ed the pressure measurement by 30 minutes The standard instructions were as follows

"After at least 5 minutes' rest supine at the end of the examination two successive readings are made in the right arm allowing the mercury to return to zero between readings Read to the nearest 2 mm mark and record the fourth and fifth phase diastolic"

Means of the replicate readings in each subject were used in analysis and the diastolic pressures reported here are fifth phase i e at the point of disappearance of the sound

It was not feasible to arrange for the same physicians to read blood pressures in the different countries This would not, in fact, have been desirable because of language limitations and the inevitable reactions of the subjects to examination by a foreign doctor However within countries the same physicians were generally involved in the examinations in the different areas Dalmatia and Slavonia in Yugoslavia Crete and Corfu in Greece etc

In general two physicians worked simultaneously in the physical examinations taking alternate subjects so that each reported on a supposedly random sample of men in the area In some cases three or more physicians rotated in the parallel examination lines It is instructive to compare the observers in terms of the distributions of blood pressures they reported Figures B1—B12 summarize such comparisons by giving the cutting points for the 20th 50th and 80th centiles for both systolic and diastolic blood pressure in the subjects grouped by age The observers are identified by letters at the 80th centile points on the charts N=number of subjects

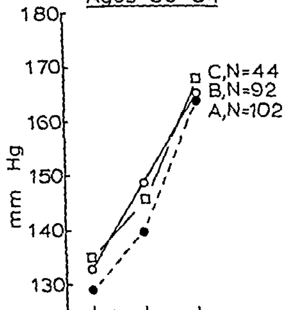
In some areas discrepancies between observers were small but significant For example at Crevalcore Observer A consistently reported higher diastolic pressure at the 80th centile than did Observer B while Observer C tended to be intermediate On the average at the 80th centile for diastole A s reading is 5 5 mm higher than B s At Crevalcore the systolic pressure distributions showed no clear trend to differ among observers

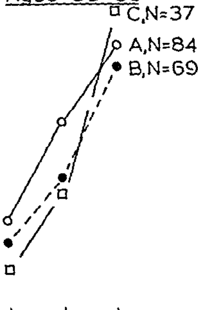
At Velika Krsna compared with Observer B Observer A tended to read higher values at the lower end of the distribution but lower values at the upper end particularly in diastole

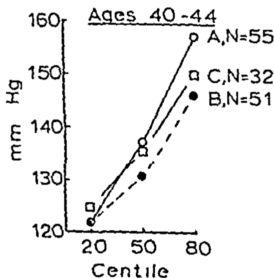
Great discrepancies among observers were noted in Greece, Finland Dalmatia and Slavonia In West Finland discrepancies in the distributions were small for diastolic pressure but very large for systolic pressure at the 80th centile in systole the average for Observer B was 14 5 mm higher than that of Observer A In Corfu Observer A s readings were substantially higher than those of Observer B at all ages in both systole and diastole Similar consistent differences are apparent in the data from Dalmatia and in Slavonia In Slavonia the 80th decile for diastolic blood pressure in B s distribution averaged 10 3 mm higher than in A s distribution

Such differences among observers as noted here have a large effect on the reported prevalence of hypertension For example if a diastolic pressure of 90 mm or more is taken as the criterion it is noted that at Corfu Observer A s men aged 50—59 (N=127) have a prevalence of 34 per cent hypertension while for B s 166 men the prevalence is only 13 per cent the difference has very high statistical significance (chi-square = 16 46) There is no way of knowing which observer is more nearly correct Conceivably one observer s bias could account for the whole discrepancy it is equally possible that both observers were biassed but in opposite directions Since A and B examined roughly equal numbers of

SYSTOLIC BP CREVALCORE







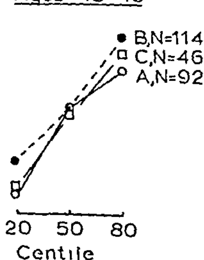


Figure B1

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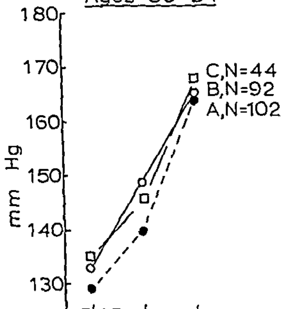
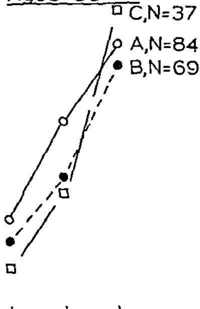
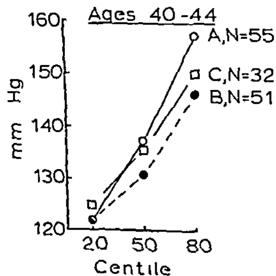






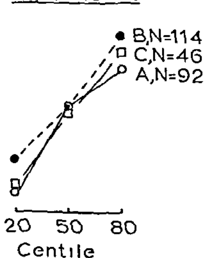
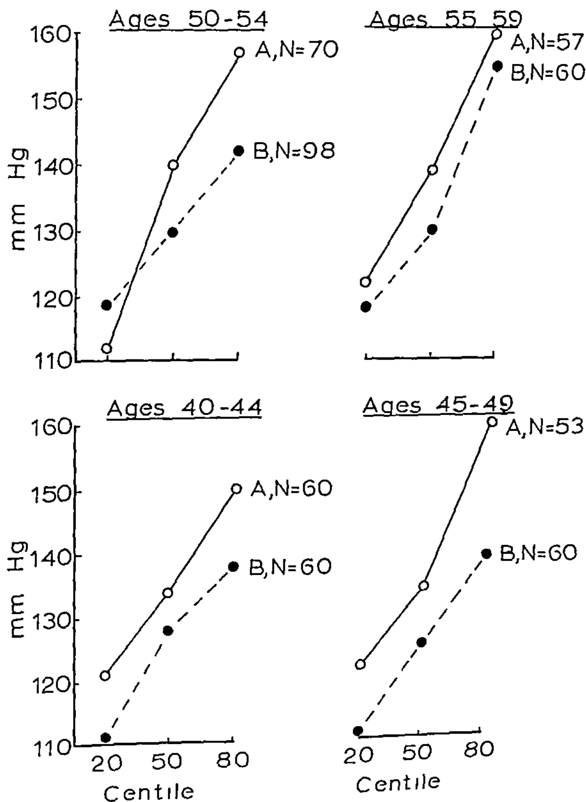


Figure B1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Ages 50-54
A, N=70
B, N=98
Ages 55 59
A, N=57
B, N=60
Ages 40-44
A, N=60
B, N=60
Ages 45-49
A, N=53
B, N=60
mm Hg
160
150
140
130
120
110
20
50
80
Centile

Figure B2

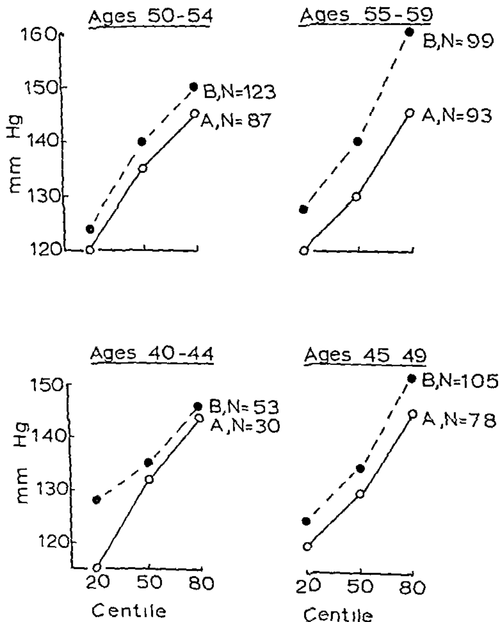

SYSTOLIC B P DALMATIA
Ages 50-54
Ages 55-59
Ages 40-44
Ages 45 49
B,N=123
A,N=87
B,N=99
A,N=93
B,N=53
A,N=30
B,N=105
A,N=78
mm Hg
160
150
140
130
120
20
50
80
Centile

Figure B3

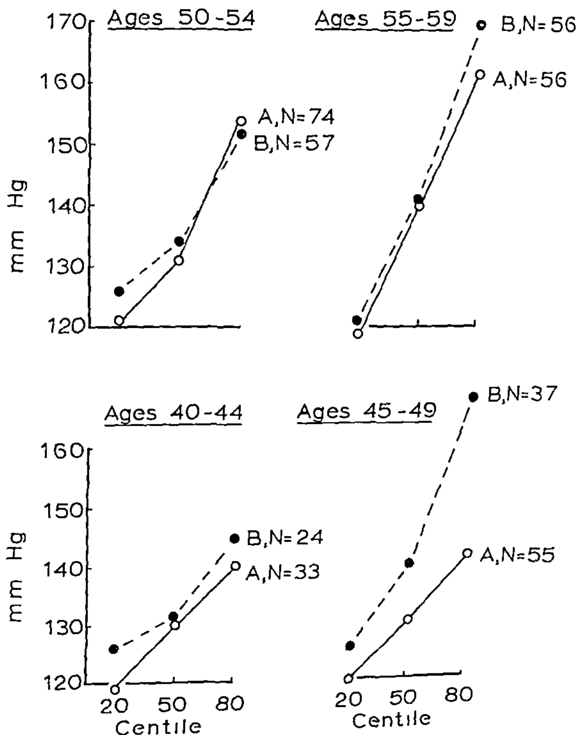
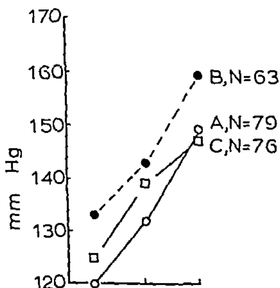
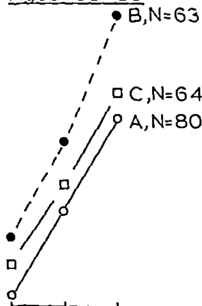
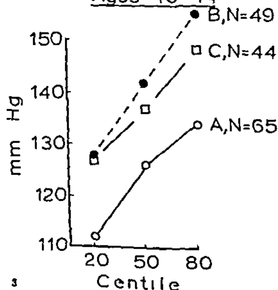

SYSTOLIC B P SLAVONIA
Ages 50-54
Ages 55-59
Ages 40-44
Ages 45-49
mm Hg
170
160
150
140
130
120
A,N=74
B,N=57
B,N=56
A,N=56
B,N=24
A,N=33
B,N=37
A,N=55
20 50 80
Centile

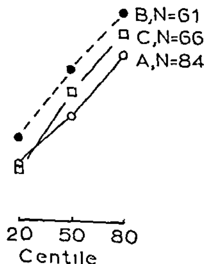
Figure B4

SYSTOLIC B P WEST FINLAND









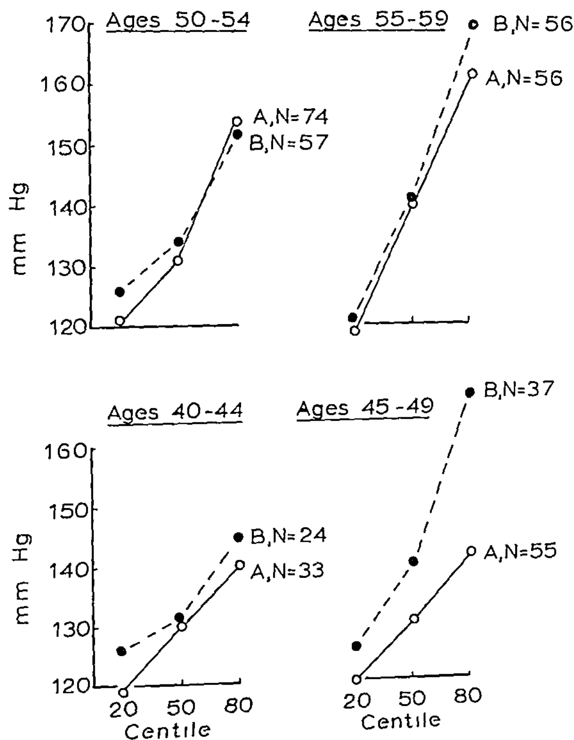
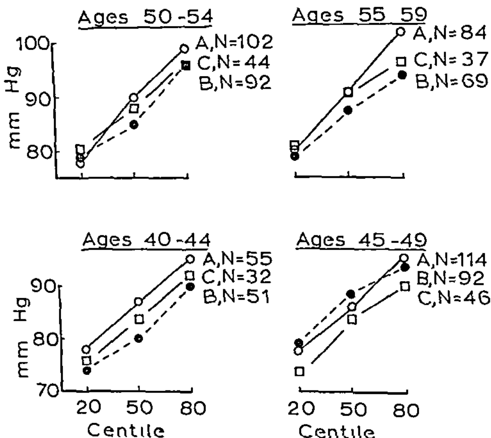

SYSTOLIC B P SLAVONIA
Ages 50-54
Ages 55-59
170
160
150
140
130
120
mm Hg
A,N=74
B,N=57
B,N=56
A,N=56
Ages 40-44
Ages 45-49
160
150
140
130
120
mm Hg
B,N=24
A,N=33
B,N=37
A,N=55
20
50
80
Centile
20
50
80
Centile

Figure B4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A,N=102
C,N=44
B,N=92
Ages 55 59
A,N=84
C,N=37
B,N=69
Ages 40-44
A,N=55
C,N=32
B,N=51
Ages 45-49
A,N=114
B,N=92
C,N=46
mm Hg
100
90
80
70
20
50
80
Centile

Figure B7

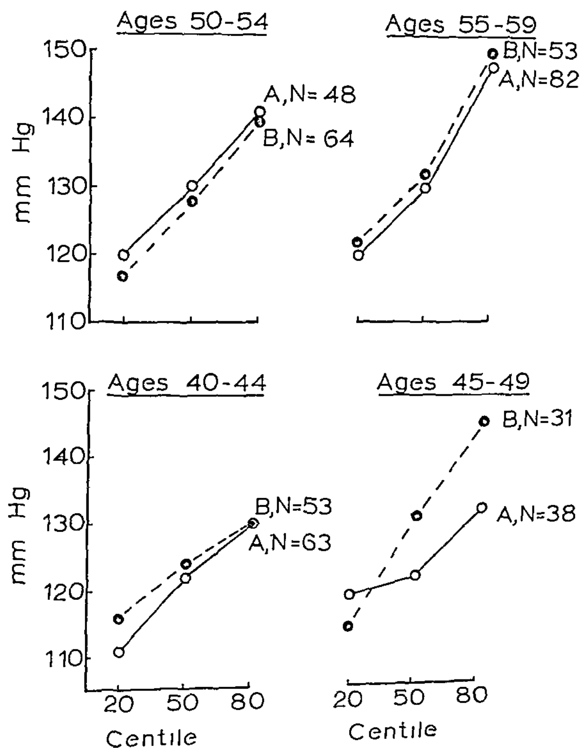

SYSTOLIC B P VELIKA KRSNA
Ages 50-54
Ages 55-59
Ages 40-44
Ages 45-49
150
140
130
120
110
mm Hg
A,N= 48
B,N= 64
B,N=53
A,N=82
B,N=53
A,N=63
B,N=31
A,N=38
20 50 80
Centile

Figure B6

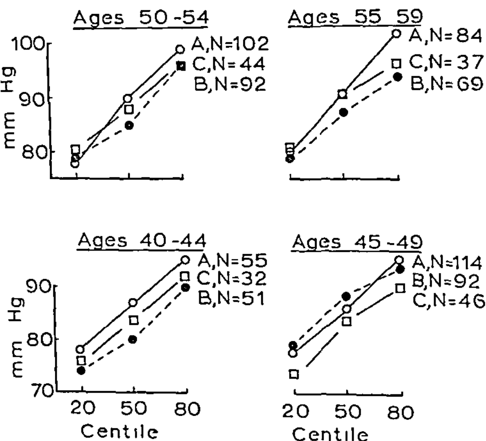
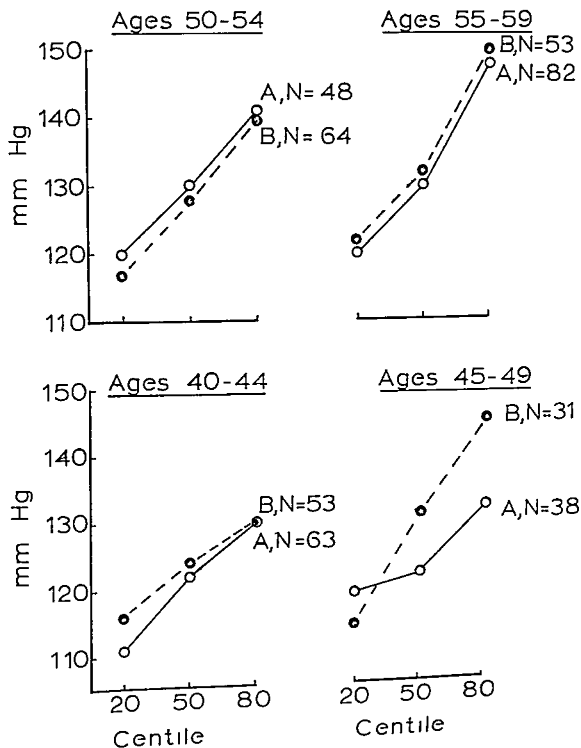

DIASTOLIC BP CREVALCORE
Ages 50-54
A,N=102
C,N=44
B,N=92
Ages 55 59
A,N=84
C,N=37
B,N=69
100
90
80
mm Hg
Ages 40-44
A,N=55
C,N=32
B,N=51
Ages 45-49
A,N=114
B,N=92
C,N=46
90
80
70
mm Hg
20 50 80
Centile
20 50 80
Centile

Figure B7



SYSTOLIC B P VELIKA KRSNA
Ages 50-54
Ages 55-59
Ages 40-44
Ages 45-49
mm Hg
150
140
130
120
110
A,N= 48
B,N= 64
B,N=53
A,N=82
B,N=53
A,N=63
B,N=31
A,N=38
20
50
80
Centile

Figure B6

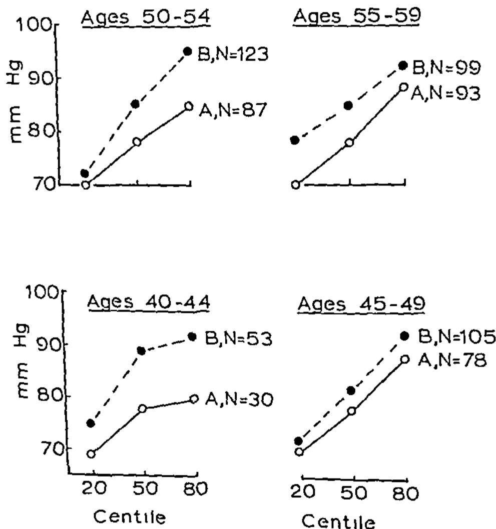

DIASTOLIC B P DALMATIA
Ages 50-54
Ages 55-59
Ages 40-44
Ages 45-49
mm Hg
100
90
80
70
B,N=123
A,N=87
B,N=99
A,N=93
B,N=53
A,N=30
B,N=105
A,N=78
20 50 80
Centile

Figure B9

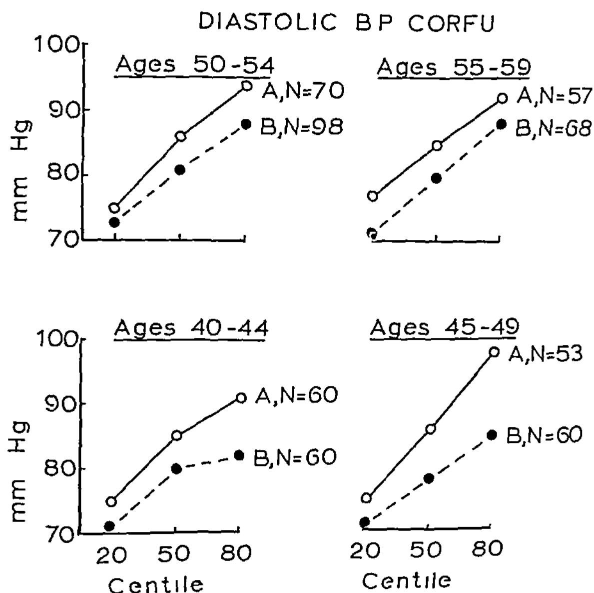

DIASTOLIC BP CORFU
Ages 50-54
Ages 55-59
Ages 40-44
Ages 45-49
A,N=70
B,N=98
A,N=57
B,N=68
A,N=60
B,N=60
A,N=53
B,N=60
100
90
80
70
mm Hg
20 50 80
Centile

Figure B8

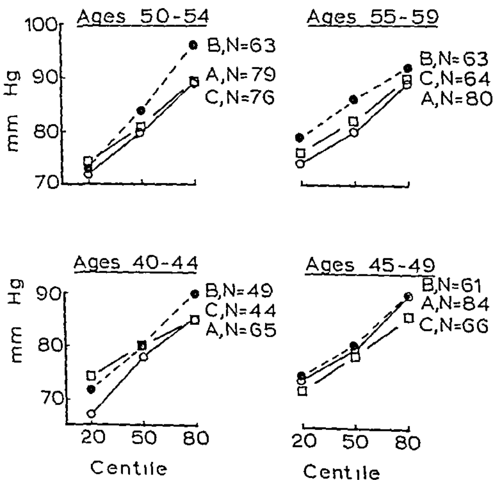

DIASTOLIC B P WEST FINLAND
Ages 50-54
100
90
80
70
mm Hg
B,N=63
A,N=79
C,N=76
Ages 55-59
B,N=63
C,N=64
A,N=80
Ages 40-44
90
80
70
mm Hg
B,N=49
C,N=44
A,N=65
20 50 80
Centile
Ages 45-49
B,N=61
A,N=84
C,N=66
20 50 80
Centile

Figure B11

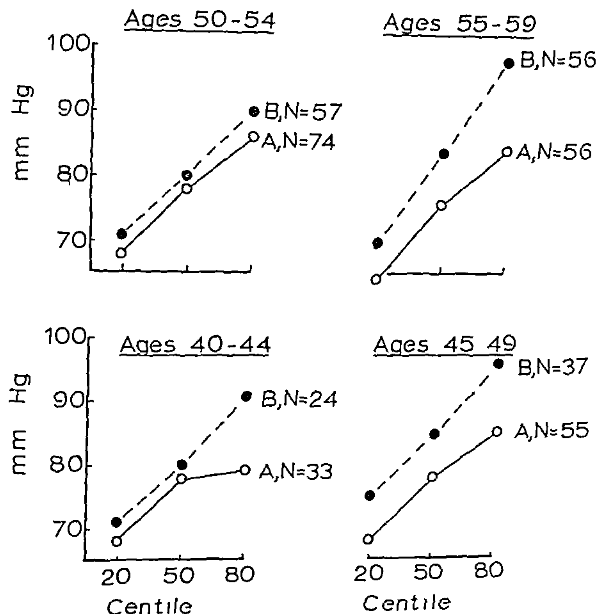

DIASTOLIC BP SLAVONIA
Ages 50-54
Ages 55-59
Ages 40-44
Ages 45 49
100
90
80
70
mm Hg
B,N=57
A,N=74
B,N=56
A,N=56
B,N=24
A,N=33
B,N=37
A,N=55
20 50 80
Centile

Figure B10

men the reported combined prevalence of about 23 per cent hypertension by this criterion could be anywhere from 68 to 177 per cent of the true prevalence

This analysis of discrepancies between observers indicates the need for great caution in comparing countries in regard to blood pressure distribution or the prevalence of hypertension Comparisons between areas where the same physicians measured the blood pressure is much safer of course And discrepancies between observers within a single area should not seriously distort relationships within that area between blood pressure and other variables In effect the result of observer differences would be that of introducing a large but presumably randomly distributed error

Practically all published records of individual blood pressure show digit preference with the terminal digit zero being much the most frequent and five being the next in popularity The records from the present series all show a strong preference for terminal zero Figure B13 summarizes the frequency of reporting the terminal digits in the systolic blood pressure readings Such digit preferences limit the possibilities of detailed analysis of blood pressure distributions but should not seriously distort relationships between blood pressure and other variables Further mere avoidance of digit preference is no guarantee of accuracy in the reading

3 Serum Cholesterol

Blood samples were drawn with a minimum of stasis from a vein in the antecubital fossa of the arm the subjects were not required to be in the basal fasting state After being allowed to clot for at least 30 minutes the bloods were centrifuged and the serum was taken off With exceptions noted below 0 1 ml portions were measured onto filter paper (Whatman no 1 or equivalent) the filter papers were hung up in room air until dry (1 to 3 hours) before being packed in envelopes and sent by letter mail to the central laboratories in Minnesota or in Naples for analysis by the method of Abell *et al* (1952) as modified by us (Anderson and Keys 1956)

This method includes hydrolysis of the cholesterol esters with alcoholic KOH After hydrolysis total cholesterol is extracted from the alcoholic solution by shaking with petroleum ether The solvent is evaporated from the petroleum ether solution by a stream of warm air fresh Liebermann-Burchard reagent is added and the color is developed and read under specified conditions of time and temperature Blanks and reference serum standards are processed in the same way and are included in each batch of analyses If pure cholesterol or reference serum standards are not carried through with filter paper the calculated results from unknowns are about 4 per cent too low

This method applied to either fresh serum or to serum dried on filter paper gives results that tend to be 1 to 2 per cent higher than those obtained with the most careful estimation using digitonin precipitation This slight discrepancy is attributed to tiny losses of the digitonin precipitate in transfer

The results are about 15 per cent lower than those obtained with the old Bloor and similar methods that do not involve hydrolysis of the cholesterol esters and use pure cholesterol standards The reason for this discrepancy is the fact that the Liebermann-Burchard reagent gives a more intense color with cholesterol esters than with free cholesterol The ratio of ester to free cholesterol is remarkably constant in blood serum except in some serious disorders that are generally readily

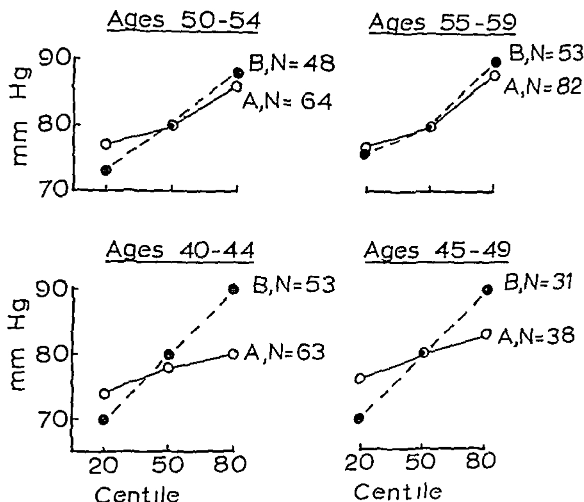

DIASTOLIC B P VELIKA KRSNA
Ages 50-54
Ages 55-59
Ages 40-44
Ages 45-49
mm Hg
90
80
70
B,N=48
A,N=64
B,N=53
A,N=82
B,N=53
A,N=63
B,N=31
A,N=38
20 50 80
Centile

Figure B12

recognized and Bloor analysis results on fresh serum can be corrected to true total cholesterol concentration from the following considerations

In a series of 134 serum samples analyzed in duplicate with the Bloor method and with the present method least squares analysis gave the result

$$Y=0\,827X+2\,58$$

where Y is cholesterol (mg per 100 ml) by our method and X is the value by the Bloor method The standard error of estimate for this equation was $\pm$ 10 14 If it is insisted that the line must go through the zero-zero origin the least squares solution is $Y=0\,836 \pm 10\,23$ Hence Bloor values obtained by analysis of fresh serum shortly after blood sampling can be corrected by the multiplication factor 0 836 This may not be true with serum subjected to prolonged storage because auto-hydrolysis reduces the proportion of ester cholesterol

Prolonged storage in air at room temperature of serum dried on filter paper results in alteration of some of the cholesterol molecules This can be shown by column chromatography which separates the cholesterol and its derivatives into fractions differing in the intensity of color produced by the Liebermann-Burchard reagent Fortunately the net color intensity is unchanged with the method used here though great changes are noted when ferric ion intensification of the color is used

Exceptions to the practice of making all analyses on dried serum were the Zutphen series in which analyses of fresh serum were made locally in addition to the analyses of the dried serum in Minnesota and at Tanushimaru and Ushibuka where fresh serum after saponification was analysed by the method of color development with ferric ion intensification (cf Zlatkis et al 1953 Henley 1957) A few checks made on dried serum samples sent from Japan to Minnesota indicated only fair agreement so the cholesterol values reported here from the Japanese samples may not be perfectly comparable with the other series

The reliability of the cholesterol method as measured in Minnesota was tested over a period of three years during which blind analyses were made of serum samples supplied by the Communicable Disease Center of the U S Public Health Service at Atlanta Georgia The standard errors of measurement were reported by the Atlanta center in none of those series of tests did S E M exceed ± 5 mg cholesterol per 100 ml $(S\,E\,M)^2 = (\Sigma\Delta^2)\ /2N$ where Δ is the difference between analyses of duplicates and N is the number of pairs

The comparability of the results from the Minnesota and Naples laboratories has been checked for many years by frequent exchange of duplicates including batches of lyophilized plasma or serum which serve as common reference materials Table B3 summarizes results with two different batches one sampled reconstituted and analyzed in 1963 7 times in Minnesota and 25 times in Naples the other in 1965 11 times in Minnesota and 27 times in Naples

Among methods for checking the comparability of cholesterol analyses on liquid plasma or serum and on the same material dried on filter paper and then subjected to analysis one device is to sample periodically a batch of lyophilized plasma reconstitute this and analyze one portion in the liquid state and analyze another portion after first drying it on filter paper The lyophilized material is stored at room temperature between samplings The results from such tests on 4 batches of material are given in Table B4 The data show essential identity of results from both dried and liquid material and also demonstrate the stability of

SEDENTARY CLERKS
SWITCHMEN
ROME RAILROAD
DALMATIA
SLAVONIA
ZUTPHEN
CREVALCORE
MONTEGIORGIO
VELIKA KRSNA
E FINLAND
W FINLAND
TANUSHIMARU
CRETE
CORFU
USHIBUKA

PER CENT FREQUENCY
0 10 20 30 40 50

0123456789 0123456789 0123456789
TERMINAL DIGIT

cholesterol in the lyophilized material for as long as a year

Repeatability of the cholesterol values from the analysis of 0 1 ml serum samples dried on filter paper is substantially as good as the repeatability of values on liquid serum The best test of course is to repeat the analysis on two different occasions recording the values blind i e without knowledge of the first result when the second analysis is made Four series of such tests covering 62 samples are summarized in Table B5

In the first several years (1955 1956) of trial of the method of cholesterol analysis on 0 1 ml serum spots dried on filter paper and transmitted by mail to a central laboratory for analysis analyses were made on the fresh serum at the point of collection and the dried duplicates were later analyzed without knowledge of the results on the fresh serum The results of two such tests are given in Table B6 Analysis of the dried samples from Naples was completed in 3 weeks after the blood was drawn and dried in the field In the case of the 126 samples from Cape Town the storage period was 3 to 5 weeks for half of the samples but the other half were delayed (because of insufficient postage) and were analyzed 3 to 4 months later In all cases however the dried and fresh sample results agreed satisfactorily the mean difference being 1 6 mg per 100 ml in the Cape Town material and 0 2 in the Naples material These trivial average differences represented slightly higher values in the dried material than in the fresh serum Results of special storage tests are in Table B7

Before the start of the surveys reported here exhaustive tests were made of the comparability of casual blood samples with blood samples drawn in the fasting state early in the morning The results of such tests are given in Table B8 No significant difference was found between fasting and nonfasting samples in these tests It is notable that even when breakfast included an extremely large dose of cholesterol added to a cholesterol-rich breakfast the post meal sample was only slightly higher in cholesterol (3 95 mg per 100 ml) than the pre breakfast sample

4. Electrocardiography

The reasons have been detailed for the attempt to characterize these populations by electrocardiography (ECG) (Blackburn *et al* 1960) as have been the problems in standardized application (Blackburn 1965) The instruments and procedures employed in these studies in efforts to reduce the variability of the ECG are here outlined

Instruments Multichannel, direct-writing research type instruments were used in all areas as they were found to be sufficiently portable rugged and stable in operation with adequate response at the low and high ends of the frequency spectrum and they considerably facilitated rapid recording of the resting and post-exercise tracing Two- three- and four-channel models of the Elema Siemens Schwarzer Phillips and Sanborn machines were employed Calibration and paper speed were controlled and records made routinely at 25 mm /sec. speed

Procedure was standard in all areas and consisted of a supine resting record made of leads I II III aVR, a VL, aVF V_{123456} after at least 30 minutes avoidance of eating heavy activity or smoking Room temperature was comfortable for men unclothed to the waist The skin was prepared by cleaning with a fat solvent and vigorous rubbing followed by application of electrode jelly or paste One to six per cent of the subjects in most areas were

TABLE B3

Cholesterol analyses in Minnesota and in Naples Lyophilized reference serums reconstituted, and independently analyzed, in Minnesota and in Naples N = number of samples analyzed

MATERIAL	MINNESOTA			NAPLES		
	N	Mean	S E	N	Mean	S E
1963 Reference	7	152 4	0 48	25	153 0	0 33
1965 Reference	11	148 5	0 55	27	147 9	1 02

TABLE B4

Cholesterol values mg per 100 ml from analyses of four batches of lyophilized plasma repeatedly reconstituted and analyzed in the liquid state and also after the liquid was dried on filter paper before analysis N = number of reconstituted samples independently analyzed

BATCH	PERIOD COVERED	LIQUID				DRIED			
		N	Mean	S D	S E	N	Mean	S D	S E
3 57	12 Mos	10	211 0	2 04	0 65	16	212 9	5 42	1 36
10 58	2 Mos	10	173 6	6 86	2 17	10	175 0	6 00	1 90
8 59	2 Mos	7	243 3	5 55	2 09	7	240 7	7 07	2 68
7 60	6 Mos	8	208 4	4 36	1 54	20	204 7	5 01	1 07

cholesterol in the lyophilized material for as long as a year

Repeatability of the cholesterol values from the analysis of 0 1 ml serum samples dried on filter paper is substantially as good as the repeatability of values on liquid serum The best test of course is to repeat the analysis on two different occasions recording the values blind i e without knowledge of the first result when the second analysis is made Four series of such tests covering 62 samples are summarized in Table B5

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Procedure was standard in all areas and consisted of a supine resting record made of leads I II III aVR a VL, aVF $V_{1\,2\,3\,4\,5\,6}$ after at least 30 minutes avoidance of eating heavy activity or smoking Room temperature was comfortable for men unclothed to the waist The skin was prepared by cleaning with a fat solvent and vigorous rubbing followed by application of electrode jelly or paste One to six per cent of the subjects in most areas were

TABLE B5

Cholesterol analyses of 0 1 ml serum dried on filter paper Duplicates independently analyzed on different occasions Values in mg per 100 ml

SOURCE	N	FIRST		SECOND		S E M
		Mean	S E	Mean	S E	
Yugoslavia	20	130 8	3 57	130 8	3 67	2 59
Greece	22	145 0	5 58	145 8	5 76	2 18
Yugoslavia	10	214 1	15 56	211 4	14 65	4 93
Netherlands	10	233 3	11 78	237 0	11 72	3 85

TABLE B6

Comparison of cholesterol values mg per 100 ml from analyses of fresh serum and of 0 1 ml aliquots dried on filter paper and analyzed in Minnesota 3 to 6 weeks later N = number of samples

FRESH SERUM Analyzed at	N	FRESH SERUM		FRESH - DRIED	
		Mean	S E	Mean	S E M
Cape Town	126	196 1	6 3	-1 6	7 0
Naples	112	175 2	3 7	-0 2	4 9

TABLE B7

S abılıty of cholesterol ın serum dried on filter paper and stored ın envelopes at room temperature '%' ıs the average value from the stored spots as percentage of the average value obtained ın the orıgınal analyses on the fresh serum N = number of samples

STORAGE (Weeks)	N	%	STORAGE (Weeks)	N	%
3	3	99	5	3	100
4	3	96	16	3	99
5	8	101	18	3	94

TABLE B8

Absence of sıgnıficant effect of breakfast on serum cholesterol concentration ın men The Before sample was drawn ın the a m fasting state a heavy breakfast was then eaten and 2 hours later the 'After" sample was taken All values ın mg cholesterol per 100 ml serum

N	BEFORE Mean	AVERAGE Δ Before After	S E of Δ	S E M
66	206 4	2 91	1 39	8 75
12	20~ 0	0 00	2 96	7 24
21	256 4	+4 38	2 03	7 59
73*	216 4	3 95	1 37	8 77

*Breakfast for these 73 businessmen aged 50 60 included 10 000 mg of cholesterol added to a 2 egg omelette

excluded from a standard exercise test because of manifest heart disease In the oldest age group among U S railroad men 20 per cent were excluded and among East Finland men 24 per cent for the same reason The remainder performed a single step test (12' or 30 cm in height), mounting and descending to a metronome count, 20 ascents per minute for 3 minutes Immediately (30 sec to 1 minute) after completion of the step test leads I II aVL aVF V_{3-6} inclusive were recorded in the supine position In those with any suggestion of early change a 3- to 4-minute recovery record was made The procedure varied only in the study on U S railroad employees in which the work load was a 3-minute treadmill walk at 3 m p h and 5 per cent grade

Records were labelled with the name subject number study code and date and each contained notes if and why the exercise test was incomplete and a 1 mV calibration signal Records were mounted on stationery-sized cardboard and if pressure sensitive were covered by cellophane Ink-written records were folded into numbered envelopes

Classification In the absence of a generally applicable means of precise measurement of the ECG a classification system was developed to characterize more objectively the ECG items of diagnostic or prognostic interest (Blackburn *et al* 1960) This system provides clearly defined quantitative criteria for codifying major and minor variations in Q waves axis peak amplitudes S-T and T findings A-V and ventricular conduction defects and arrhythmias

Records in these first-round studies were scanned independently by 2 or 3 medical readers experienced in use of the code at the rate of 30 to 60 cases per hour and all codable items were tabulated for the record of each subject All disagreements were arbitrated by the readers met together Considerable information is available on the degree of observer variation encountered in coding by this system (Blackburn *et al* 1960 Higgins, *et al* 1963, Kagan 1965, Blackburn 1965) The experience within a laboratory is considerably better than between laboratories when no formal training in use of the code has been involved Within a laboratory repeated trial comparisons yield figures on agreement (between two observers about the presence of a codable ECG finding) on the order of 70 per cent for detailed subclasses, 80 per cent for general classes and 90 per cent for the results of the system of an adjudicated third reading

Explicit coding procedures and more recent experience in reading by clerks and paramedical personnel are available (Kagan 1965 Rose and Blackburn 1966)

5 Statistical Methods and Data Processing

All measurement data were put on IBM or Remington-Rand punch cards for analysis with counter-sorter machines and electronic computers at the University of Minnesota

For statistical analysis the men in each area or occupation group were generally grouped by quinquennia of age (40—44 45—49 50—54 55—59) and the complete distribution of each variable was obtained for each of these groups For many purposes the men in each of these age-area groups were classified into deciles with respect to each variable the decile cutting points for the variables plus those for the 5th and 95th centile adequately describe the distributions Ordinary means and standard deviations were also computed though the non-normality of some of the distributions limits the utility of these statistics

One of the variables that departs most from the normal distribution is the sum of the skinfolds this has an unusually high degree of skewness to the right and has a lower limit of 3 to 4 mm No simple transformation of this variable could be found to produce entirely satisfactory normalization but a transformation was developed which produces distributions of the transformed sums of skinfolds that are very close to normality (Kihlberg and Keys to be published) For the purpose of estimating the significance of differences in the distributions of a given variable in two population groups chi-square tests or tables of the summed binomials applied to the numbers of men segregated by a series of common cutting points were frequently made in preference to t or F tests in order to avoid assumptions about the character of the distributions Yates correction was applied in all chi-square calculations All chi-squares mentioned in the text and tables are values with one degree of freedom Table B9 gives probabilities associated with selected chi square values and will facilitate interpretation where probabilities are not specifically set forth In general the convention has been adopted of considering p values of 0 05 or smaller as "significant" i e requiring rejection of the null hypothesis that the variables under consideration are unrelated (independent)

Classification of the men by deciles of the distribution of all men of the same age in the same area has several advantages For example it is thus easy to combine age groups so as to identify the men in an area who are in the top 10 or 20 per cent of the distribution of men all of equal age (within a range of 5 years) in respect to a given variable This can provide adequate numbers for the examination of various questions about the relationships among variables on an age free basis

A frequent application of the decile classification was in regard to the search for relationships such as between hypertension" suitably defined and relative body weight or serum cholesterol A simple plot of the number of hypertensive men against decile class (number or percentage of hypertensive men on the ordinate in each decile class of the other variable on the abscissa) at once makes visible trends (which may be curvilinear or rectilinear) or the absence of a trend (indicated by a series of points approximating a random distribution about the horizontal line of the average number of hypertensive men per decile class) The significance of such trends is readily estimated by the chi-square test

Coefficients of correlations are not conspicuous among the statistics presented here In many cases misleading answers or erroneous conclusions result from the computation of the ordinary product moment coefficient That calculation concerns only linear relationships and it involves assumptions about the character of the distributions But many of the relationships of interest are not linear and many of the distributions are not normal

Examples where a different approach is much more revealing than the usual correlation analysis are shown in several sections below particularly in Sections F and G Relative body weight is importantly related to smoking habits but a coefficient of correlation between relative weight and amount smoked can be grossly misleading Blood pressure is related to skeletal shape but ordinary correlation analysis would scarcely suggest this In many situations major biological and medical interest concerns relationships towards the ends of the distributions We have attempted to focus on this by examining the distribution of men in the tops and bottoms of the arrays of the two variables

TABLE B 9

Critical values of chi-square with one degree of freedom calculated from two-by-two tables Probabilities are those of obtaining, as a result of chance deviation from expectation, values of chi-square as large or larger than those shown when the variables of interest are independent

CHI-SQUARE	PROBABILITY	CHI-SQUARE	PROBABILITY
2 71	0 10	6 64	0 01
3 24	0 07	7 88	0 005
3 84	0 05	10 83	0 001
5 02	0 25	12 12	0 0005

concerned Two by-two tables of numbers of men in decile classes 1 2 and 9 10 *for each* of two variables repeatedly showed highly significant differences that were missed by simply comparing mean values or calculating correlation coefficients Examination of the shapes of distributions and their relative locations in different age groups or samples is conveniently accomplished by plotting cumulative frequencies on arithmetic probability scales Such plots are easily identified by their non-uniform but symmetrical ordinate scales A normal distribution when so plotted appears as a straight line with slope in direct *relation to the standard deviation of the* distributions Non-normality is indicated by a curved line plot and the direction of skewness can be inferred from the curvature

Many pairs of variables (x y) were subjected to regression analysis where one of the variables (y) is expressed as a linear function of the other (x) thus

$$y^* = a + bx$$

The regression (or slope) coefficient b tells how much on the average y will increase for an increase of x by one unit Most commonly b is determined so that the sum of the squares of the deviations of the actual y values from the predicted y^* values is as small as possible In some situations however it is useful to compute the regression coefficient so that variations in both x and y directions are minimized at the same time (Cramer 1946) This orthogonal regression coefficient b^* represents the main axis of the elliptical x y configuration so that if x increases by one unit y^* increases by b^* units if y increases by one unit x^* will increase by $1/b^*$ units

6 Samples

The General Question of Samples

In the present study samples of middle aged men were studied in various regions of a number of countries No pretence is made that these samples truly represent whole large regions let alone the countries concerned However there is no reason to suggest that the samples of rural men are in any way atypical of the men in the general areas of their residence For example the sample of men in East Finland (Karelia) covered all men of prescribed age in a defined area centering at Ilomantsi it is not a random sample of men in all of East Finland But there is no basis to suggest that the sample seriously misrepresents the generality of rural men in Finnish Karelia

From long experience and careful consideration the conclusion can be defended that it is not actually possible to draw and examine in detail a strictly random sample of any large population in such epidemiological work. Data on the population distribution is seldom accurate enough and fully up to date to draw a perfect sample even on paper And when the attempt is made to examine in detail the persons in the theoretical sample the percentage of non respondents is always very substantial except in such favorable spots as villages similar to those involved in the present study

A response rate of as high as 80 per cent would be very good in cities but this is far from enough to provide an accurate inventory of disease prevalence especially when the response or lack of it is influenced by the presence of the diseases in question On the other hand even a relatively poor response rate does not necessarily mean a biased sample in regard to many

attributes and relationships between attributes

In the present studies emphasis is put on such questions as these Does blood pressure tend to be related to serum *cholesterol level? Is body fatness related* to skeletal shape? How do smokers compare with non-smokers in relative body weight? Insofar as common patterns in the answers to such *questions emerge from 18 such* widely disparate samples inferences can be made about apparently universal relationships Insofar as answers from the several samples are clear but disparate *for different samples the results* point for the need of further studies to discover underlying influences the explanation will not emerge from repetitions with 'better" samples but *from the search for and* consideration of other interrelated variables

Sample Bias from Examination Refusals

The high examination coverage achieved in these cooperative studies provide data for consideration of the *situation in which the respondents form* a small percentage of the sample In population surveys involving detailed medical examination the final coverage is usually well under 90 and may be as *little as 50 per cent of the sample* Though in the latter case it is doubtful whether the sample is often usefully representative it is important to consider the common situation where 15 to 30 per cent of the persons in the sample do not respond

Much depends on the variables of interest *of course* and *in some* situations practically complete coverage is required to assure that the prevalence of the variable in the invited sample is accurately reflected If the invitees fear that revelation of a defect or disease in the examination may carry economic or social penalty, those who know or suspect they may have the defect or disease will tend to refuse examination But even in this circumstance some indication of the extent of the bias will be given by comparing the findings on the most reluctant examinees with those who volunteered more readily

In our first survey in 1957 of men aged 45—64 at Nicotera in southern Italy all men of those ages were invited to avail themselves of what was assured to be a painless and confidential examination the community leaders — officials priests doctors teachers and the most respected men — publicly urged participation place and time of examination were arranged to be convenient About ten per cent of the men on the roster the "eager beavers' presented themselves at the first opportunity, thereafter men registered with no great pressure until about three-fourths of the roster was covered *increasing efforts at persuasion brought* the coverage up to about 85 per cent and then a concerted drive of public pressure and inducement was required to reach the 96 1 per cent coverage *finally achieved*

Similarly, in the villages of Crete in 1957 very high coverage was finally achieved (91 4 per cent) but the last 20 per cent to be examined were *decidedly reluctant* and came in only as a result of heavy community pressure from the village officials priests teachers and other leaders *In Crete* as at Nicotera some information about state of apparent health working habits etc was obtainable about the men who remained obdurate Except *for one man at Nicotera there* was no ground for any suspicion that cardiovascular disorder was present in any of the men who were not examined

Accordingly for these two samples it is interesting to compare the early or non-reluctant volunteers with those

TABLE B 10

Age distribution of respondents by number of men among occupation matched farmers The 59 most reluctant volunteers at Nicotera are compared with the 59 men in that village who came in first and the 85 most reluctant respondents in Crete are compared with the first 65 village matched men who responded to the invitation

SAMPLE	45-49		50-54		55 59		60 64	
	Early	Late	Early	Late	Early	Late	Early	Late
Nicotera farmers	25	22	16	14	11	12	7	11
Crete farmers	15	16	37	32	15	18	20	20
Both samples	40	38	53	47	26	30	27	31

TABLE B 11

Ready versus reluctant volunteers for medical examination Comparison of 59 early with 59 reluctant men in Nicotera Italy surveyed in 1957 and comparison of 85 late comers with 85 village-matched non-reluctant (ready) men in eleven villages on the island of Crete Greece surveyed in 1957 Column entries are numbers of men

ITEM		NICOTERA		CRETE	
		EARLY	RELUCTANT	EARLY	RELUCTANT
Relative body wt	under 90%	36	32	52	53
	90% or more	23	27	33	32
Σ Skinfolds	under 13 mm	37	31	53	52
	13 mm or more	22	28	32	33
Systolic B P	under 140 mm	42	37	59	53
	140 mm or more	17	22	26	32
Diastolic B P	under 90 mm	50	47	72	66
	90 mm or more	9	12	13	19
E C G	normal	46	37	59	66
	abnormal	13	22	26	19

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Much depends on the variables of interest of course and in some situations practically *complete* coverage is required to assure that the prevalence of the variable in the invited sample is accurately reflected *If the invitees* fear that revelation of a defect or disease in the examination may carry economic or social penalty, those who know or suspect they may have the defect or disease will tend to refuse examination But even in this circumstance some indication of the extent of the bias will be given by comparing the findings on the most reluctant examinees with those who volunteered more readily

In our first survey in 1957 of men *aged 45—64 at Nicotera in southern* Italy all men of those ages were invited to avail themselves of what was assured to be a painless and confidential examination the community leaders — officials priests doctors teachers and the most respected men — publicly urged participation place and time of examination were arranged to be convenient About ten per cent of the men on the roster the "eager beavers" presented themselves at the first opportunity thereafter men registered with no great pressure until about *three-fourths of the roster* was covered increasing efforts at persuasion brought the coverage up to about 85 per cent and *then a concerted drive of public* pressure and inducement was required to reach the 96 1 per cent coverage finally achieved

Similarly, in the villages of Crete in 1957 very high coverage was finally achieved (91 4 per cent) *but the last* 20 per cent to be examined were decidedly reluctant and came in only as a result of heavy community pressure from the village officials priests teachers and other leaders In Crete as at Nicotera some information about state of apparent health working habits etc was obtainable about the men who remained obdurate Except for one man at Nicotera there was no ground for any suspicion that cardiovascular disorder was present in any of the men who were not examined

Accordingly for these two samples it is interesting to compare the early or non-reluctant volunteers with those

CI RAILROAD EMPLOYEES IN THE UNITED STATES

by *Henry L. Taylor Henry Blackburn Josef Brozek R Willis Parlin & Thomas Puchner*

Introduction

For the analysis of characteristics of railroad employees data were available on 3049 railroad employees in the northwestern quadrant of the United States who were examined in 1957—59 The data and analysis presented here concern men in statistically pre determined samples who were aged 40 through 59 years at the time of examination and who were classified as sedentary clerks (N = 860) switchmen (N = 837) and executives (N = 251)

In the U S A as in many other countries railroad employees tend to be stable in their occupations and in the employ of the industry their ossupations are relatively fixed in regard to physical activity and they have long been covered by a kind of social security system providing pensions insurance and other benefits that maintains detailed records of employment disabilities retirements and deaths In the U S A the Railroad Retirement Board operates this system and maintains the necessary records These considerations and the fact that the number of employees in the industry is large suggested that railroad employees would be particularly suitable for epidemiological studies

These advantages are accompanied by a number of problems that had to be resolved in order to organize a successful epidemiological study with railroad employees Besides obtaining the essential permission and assurance of cooperation from the railroad companies it was necessary to have agreement and help from the various labor unions involved both at the national or regional level and in each of the localities where the work was to be done The cooperation of local brotherhood officials is important in persuading men to report for examination

The cooperation of the Railroad Retirement Board is useful in many respects and is almost indispensable for evaluating the relevance of particular samples to the industry as a whole and for the analysis of the effects of withdrawals from the industry job transfers etc

Besides these questions of permission and cooperation the operation of a program that involves examination of railroad employees encounters problems because of the geographic dispersion of the men It is not possible to sample the industry properly by concentrating on a few large centers men are employed at every place where there is a railroad station and at other places along the

most reluctant the men who would have been non-respondents if it had not been possible to bring so much pressure on them In order to assure highest comparability in other respects the reluctant and non-reluctant men were matched as to village and lifelong occupation (farmers) The result was 59 reluctant men at Nicotera and an equal number of "eager" respondents and in Crete 85 men in each category

Table B10 shows the age distribution of the two sets of men contrasted in willingness to respond There is no significant trend for the reluctant respondents to differ in age distribution from those ready or eager to be examined Table B11 summarizes examination findings in these men In none of the items is there even an approach to a significant difference between the men when they were classed by willingness to volunteer for medical examination

These findings pertain to populations of men who had no reason to believe that social position or occupation or financial security would be affected by the discovery of disease other than tuberculosis However in such populations the discovery of tuberculosis means transport to a sanatorium or hospital and it is interesting that at Nicotera two of the three men on the roster known to have a history of tuberculosis refused examination

A different situation is to be expected among an employed group in which disclosure to the employer of serious cardiovascular disease would probably mean enforced disability retirement with a major reduction in income Even though the U S railroad employees were emphatically re-assured about the confidentiality of the examination results this fear probably played a role in their attitude toward participation Significantly disability retirements for cardiovascular disease in the next few years after the examination were proportionately more among the U S railroad employees who had refused examination than among those who were examined

Obviously such a disease-related bias may produce serious errors in estimates of prevalence of the disease in the population which the sample was supposed to represent It may well be that the prevalence of coronary heart disease among U S railroad employees is greater than found in the surveys the findings in those surveys must be considered to indicate minimum prevalence On the other hand there is reason to believe that in the population "chunk" surveys in Europe and Japan the non-respondents did not tend to include men who had any disability or suspicion that they might have cardiovascular disease If anything then the prevalence data may lead to very slight over-estimates if present such an error would be exceedingly small

But these surveys were not directed primarily at providing estimates of prevalence the long-range aim was to provide data on pre-disease characteristics for follow-up analysis of incidence a major short-range aim was to obtain distributions and information on interrelations among characteristics that may be involved in etiology and clinical developments of cardiovascular disease For these purposes some bias in the samples would be tolerable so long as the bias does not distort the interrelations among variables There is no reason to suspect such distorting bias in the samples studied

TABLE CI 1

The Cooperating Railroads in the Study of U S Railroad Employees (Note that railroad 1 through 16 operate completely within the area under study; railroads 17 through 20 have divisions in this area but also operate in other areas)

	RAILROAD		RAILROAD
1	Great Northern	11	Minnesota Transfer
2	Northern Pacific	12	Belt Railroad of Chicago
3	Milwaukee Road	13	Indiana Harbor Belt
4	Burlington	14	Duluth Mesabi and Iron Range
5	Chicago and Northwestern	15	Chicago River and Indiana
6	Western Pacific	16	Spokane Portland and Seattle
7	Soo Line	17	Chicago Rock Island and Pacific
8	Minneapolis and St Louis	18	Southern Pacific
9	Chicago Great Western	19	Chesapeake and Ohio
10	St. Paul Union Depot	20	St Louis and San Francisco

TABLE CI 2

Geographical areas for sampling U S railroad employees

Area I. -- Chicago and Milwaukee
Area II. - The region west of Area I to the Rocky Mountains
B - with populations of 150 000 to 1 000 000
C - 50 000 to 150 000
D - less than 50 000
Area III. -- The Rocky Mountain region
Area IV - The West (Pacific) Coast

line as well An obvious answer to the question, adopted in the present study, is the provision of mobile examination and laboratory quarters railroad cars specially fitted out for the purpose that can be moved from place to place along the railroad on a suitable schedule

The Population for Study

The cooperation of 20 railroad companies operating in the northwestern quadrant of the United States circumscribed by Chicago St Louis San Francisco and the Canadian border was solicited Only two important railroad companies operating principally in this area refused The 20 companies that agreed to cooperate included 15 line haul first class railroads 4 switching and transfer companies operating within metropolitan areas and one depot company serving a metropolitan area The study population then was drawn from these 20 cooperating companies which include all the types of organizations employing both switchmen and clerks The cooperating railroads are listed in Table Cl 1

Each company was asked to supply the names of all male clerks switchmen dispatchers and executives whose age in 1957 was 40 or more and who were employed in the summer or fall of 1957 A total of 12 586 names were delivered to the Laboratory along with the social security number location of work title of job etc A roster of the study population was then compiled showing the numbers of men employed by each railroad in the various towns and cities served by the road in question Men who were stationed at those locations where less than 10 switchmen and clerks were employed were not included in the final tabulation The number of men whose ages were 40 to 59 in the three occupations reported here (clerks switchmen executives) totaled 8 053

The men potentially available in the study population were in towns with populations as small as 5,000 and as large as several million and in regions differing in climate and other features Accordingly for the purposes of sampling and subsequent analysis areas were distinguished as indicated in Table Cl 2 The men examined in St Louis were omitted from this analysis by size of community because the number of switchmen in St Louis was very small and the characteristics of the community are such that it seemed to be illogical to combine these men with those in Chicago

Clump sampling was used A statistician selected units consisting of an installation of a particular company in a particular location Thirty units were selected in such a way as to ensure approximately proportional representation from each of the geographical areas and each of the sizes of urban area classifications

A systematic approach was made to each unit in an attempt to develop interest in and response to the program Contact was made with the general chairman for each "brotherhood" (union) for the railroad in question and he was asked to write a letter endorsing the project This letter was reproduced and enclosed with an invitation to each man at the unit to participate in the program The chairman of the local brotherhood lodge was also contacted and permission was obtained to attend a regular meeting of the lodge The meeting was advertised throughout the clerical and yard offices of the railroad in the town or facility selected The union meeting was attended by a staff member of the Laboratory the program was explained and the questions were answered It was the practice of the Laboratory staff members attending the meeting to check the

TABLE C1 1

The Cooperating Railroads in the Study on U S Railroad Employees (Note that railroads 1 through 16 operate completely within the area under study, railroads 17 through 20 have divisions in this area but also operate in other areas)

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TABLE C1 2

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union membership list against the list supplied by the railroad company Names of men who had been omitted from the invitation list but who were in the correct age group and occupation were added to the list

Personal invitations were then issued by mail to each individual on the invitation list Those individuals wishing to participate returned a letter by mail stating when they could attend the examination Clerks were examined on company time but due to operating problems it was impossible for management to extend this privilege to switchmen

Two railroad cars remodelled to serve as mobile laboratories visited each of the locations at least twice three visits were made to the large metropolitan areas where it was more difficult to persuade the men to come in for the examination On arrival at the location with the Laboratory railroad cars efforts were made to recruit all the men on the invitation list In some cases men were discovered who were not on the examination list but were in the correct occupation and age class The privilege of examination was extended to such men but they were classed as volunteers since they had not been approached in the same way as the men on the invitation lists A number of additional volunteers were examined in cases where it was believed to be useful in terms of good will and of developing an interest in the program in men influential in the local railroad community These 149 men are listed under "Self-Selected" as "other occupations" in Table C1 3

A number of special jobs were not included in the major categories of clerks or switchmen Chief clerks were not considered to be eligible for the clerk cohort since they carry a substantially larger responsibility and are paid at a higher rate For the same reasons yard masters were not included in the switchmen cohort Switchtenders were also excluded from this cohort since their physical activity level is definitely lower than switchmen as a group A substantial number of chief clerks yard masters and switchtenders appeared on the invitation lists Therefore this group of 69 men is listed under "other occupations" in the "Sample" in Table C1.3 Table C1.3 also indicates the men found to be under 40 or over 59 at the time of examination these men were not included in the later analysis presented here

Occupational Classification of Physical Activity

Physical activity was considered to be an important variable in this study and the original selection of occupations for inclusion in the study attempted to provide clear contrasts in this respect — switchmen on the one hand versus clerks executives and dispatchers on the other The category of switchmen was chosen to represent relatively high physical activity and it includes an adequate number of men However more careful scrutiny showed the situation to be more complicated than anticipated

The 129 broad occupational classifications set up by the U S Interstate Commerce Commission were reviewed in regard to physical activity It was found that the number of tasks involving physical work required of switchmen is relatively small in comparison with that of some other occupations so the general level of activity required by switchmen places them in a moderately active group In a four-level scale desk workers switchmen maintenance-of-way employees and lumberjacks can be regarded respectively as examples of sedentary moderately active active and extremely active groups

TABLF Cl 3

Distribution of examined U S railroad men. Numbers of men classed by age sample status and occupation.

OCCUPATION	SAMPLE			SELF-SELECTED		
	Under 40	40-59	Over 59	Under 40	40-59	Over 59
Clerks sedentary	15	860	82	28	63	13
Clerks non-sedentary	1	156	15	6	16	1
Switchmen	19	837	63	29	41	8
Executives	12	251	34	21	66	13
Dispatchers	8	65	13	3	3	2
Other occupations	10	69	10	34	149	32
Total	65	2238	217	121	338	69

Study of the duties of railroad employees classed as clerks revealed that a significant fraction of these men have duties that take them into the yards for the purpose of checking car numbers or on to the baggage platform where they are engaged in walking or baggage handling to such an extent that they could not be classed as sedentary employees These men therefore were classed as non-sedentary clerks and are listed under this heading in Table C1 3 Some of these clerks were as active as switchmen but a great many of them appeared to be in the grey zone which made them not active enough to be included in the moderately active class It was felt that since an important part of the program was focused on physical activity this group should be analyzed separately

Executives were found to be a mixed group some of whom spend the great majority of their time at their desks while others are relatively active in walking as required on inspection tours and in some instances in supervision of shops etc

Dispatchers are completely sedentary in their working hours The duties of a dispatcher require that he be at his desk almost continuously during the period that he is on duty These employees will be discussed in separate publications

Observations have been made of the energy expenditure of both switchmen and clerks during the working day The oxygen requirement for each of the several tasks required of men in these occupations was estimated with on-the-job direct measurements This was followed by time-and-task measurements and finally a dietary survey was carried out on a small group in each occupation Switchmen do more on-the-job work than clerks the year around the difference increasing in the winter and at certain peak load periods due to overtime Switchmen appear to average about 600 calories a day more energy expenditure than clerks in some special situations the difference may be as high as 1200 calories The detailed data will be reported elsewhere

Details of Age and Occupation Distribution

The distribution of the examined population by occupation age and sample status is presented in Tables C1 4 and C1 5 This report deals with findings in sedentary clerks switchmen and executives whose age at the time of examination was 40 to 59 inclusive and who qualified for admission to the sample i e were on the invitation list and received mailed invitations The distributions for "all U S" in Table C1 4 are based on men employed in 1954 The inclusion of men over the age of 59 in the sample is due in part to some errors in the initial rosters but mainly to the fact that the rosters were compiled in 1957 but examinations did not cover all of the men until early 1960 by which time some of the men had become over age Errors in the original reports of age by railroad companies are largely responsible for inclusion of some men under 40 in the sample A few men on the original invitation list had changed jobs by the time of examination These men are reported here as "other occupations" under "Sample" in Table C1 3

Tables C1 4 and C1 5 show that the distribution by age of the examined population the invited population and the study population are all very similar in the clerks and switchmen classes of occupation Moreover the clerks in the national population ("all U S") have much the same age distribution as the clerks in the study population On the other hand the same data suggest that the study population is

TABLE C1 4

Age distribution of U S railroad employees Numbers of men and percentages (in brackets)

OCCUPATION	POPULATION	YEAR	40-44	45 49	50 54	55 59	40 59
Sed Clerks	All U S	1954	6336 (15 9)	9769 (24 5)	1[illegible]86 (30 8)	11511 (28 8)	3990[illegible] (100 0)
	Study	1957	575 (18 2)	6[illegible]9 (19 9)	904 (28 6)	1050 (33 2)	3158 (100 0)
	Invited	1957 59	220 (18 9)	254 (21 8)	317 (27 2)	372 (32 0)	1163 (100 0)
	Examined	1957 59	167 (19 4)	185 (21 5)	240 (28 0)	267 (31 1)	859 (100 0)
Switchmen	All U S	1954	8057 (26 5)	5988 (19 7)	7553 (24 9)	8768 ([illegible]8 9)	30366 (100 0)
	Study	1957	1205 (31 6)	1004 (26 3)	800 (21 0)	808 ([illegible]1 2)	3817 (100 0)
	Invited	1957 59	449 (31 8)	391 (27 7)	275 (19 4)	299 (21 1)	1414 (100 0)
	Examined	1957 59	280 (33 5)	244 (29 2)	153 (18)	158 (18 9)	835 (100 0)
Executives	Study	1957	213 (19 8)	200 (18 6)	315 (29 2)	350 (32 5)	1078 (100 0)
	Invited	1957 59	65 (17 9)	54 (14 9)	104 (28 9)	140 (38 6)	363 (100 0)
	Examined	1957 9	48 (19 4)	35 (14 1)	68 (27 4)	97 (39 1)	248 (100 0)

TABLE C1 5

U S railroad employees classed by age and occupation men examined as % of invited sample (response) and as % of study population (representation)

OCCUPATION	ITEM	40-44	45-49	50 54	55-59	40 59
Sed Clerks	Response	75 9%	72 8%	75 7%	71 8%	73 9%
	Represent	29 0	29 4	26 5	25 4	27 2
Switchmen	Response	63 4	62 2	55 6	5 8	59 1
	Represent	23 2	24 3	19 1	19 5	21 9
Executive	Response	73 8	64 8	65 4	69 3	68 3
	Represent	22 5	17 5	21 6	27 7	23 0

not representative of the age distribution of the switchmen in the national population There is a suggestion that switchmen in the older age groups in the study population were underrepresented It is not known whether or not this is due to errors in reporting by the railroad companies or to employment practices The examined population of switchmen is proportionately smaller in the older age groups when compared to the study population Finally the response rate to the invitations is definitely smaller in the older switchmen It is clear, then, that the age distribution of the clerks is related to industry conditions while that of the switchmen is influenced by selection against the experiment

The response rate by geographical area is presented for the three occupations in Table C1 6 and the same information by size of community in Area II is contained in Table C1 7 The poorest response rate occurred in Area I (Milwaukee-Chicago) and the best in cities whose populations were less than 150 000 The very poor response of switchmen in Area I is largely due to a very low response rate (25 %) in one installation in which management-labor relations were strained and it proved impossible to capture the confidence of the switchmen

To ensure reasonable distribution of sampling and adequate numbers it was felt that at least 20 % sample of the study population roster should be examined The data on the percentage of the roster examined presented in the Tables show that this goal was reached in all cases with three exceptions 1) switchmen on the West Coast, 2) clerks and 3) switchmen in towns with population less than 50 000 in Area II (great plains west of Milwaukee and Chicago)

Executives are not classed by areas since those men are moved from one location to another during the period in which they are "moving up' in the ranks and on attaining a position in the general office do a great deal of traveling

Since atherosclerosis underlying coronary heart disease develops slowly over a long period of time it was of interest to know how long men had been in the railroad industry and in the specific occupation This information was also pertinent to follow-up studies on deaths and retirements since it was planned to obtain death certificate data and information on retirement cause from the files of the Railroad Retirement Board The Board deals with death benefits and retirements only on those men who have had ten years of service in the industry Tabulations by five-year age groups of the length of service were made The age-adjusted prevalence of men with less than ten years of service in the 40—49 decade of age was 5 5 per cent in the sedentary clerks and 6 3 per cent in switchmen In the 50—59 decade of age there were no switchmen with less than 10 years of service and only 1 4 per cent of the sedentary clerks fall into this category Executives with less than 10 years of service in the industry were found only in the 40—44 years old group where the prevalence was 6 5 per cent The median number of years in the industry for sedentary clerks was 20 5 in the 40—44 year age group 23 5 for clerks in the 45—49 year old group 32 1 in the 50—54 age group and 38 0 in the 55—59 age group In the switchmen the corresponding values at the medians were 16 8 18 9 24.3 and 33 4 for age groups 40—44 45—49 50—54 and 55—59 respectively Length of service in the principal areas did not show large variations except in the Rocky Mountain area where median values for clerks aged 40—54 were 3 to 7 years of service less than in the other areas and for switchmen aged 50—59 were

TABLE C1 6

U S railroad employees classed by geographical areas I Major Metropolitan (including Chicago and Milwaukee) II Midwestern Plains III Mountains IV West Coast Numbers are in the study population in the invited sample and of examined respondents Percentages are of men responding in invited sample and in study population

OCCUPATION	AREA	STUDY	INVITED	EXAMINED	RESPONDENTS % OF INVITED	STUDY
Clerks	I	841	388	261	67 3	31 0
	II	1433	471	365	77 5	25 4
	III	269	75	54	72 0	20 1
	IV	615	232	179	77 2	29 1
	All	3158	1166	859	73 7	27 2
Switchmen	I	1064	516	253	49 0	23 7
	II	1494	475	311	65 5	20 9
	III	352	149	106	71 1	30 1
	IV	911	274	165	60 2	18 1
	All	3817	1414	835	59 1	21 9
Executives	I	236	55	46	83 6	19 5
	II	529	200	135	67 5	25 5
	III	85	16	14	87 5	16 5
	IV	228	92	53	57 6	23 2
	All	1078	363	248	68 3	23 0

TABLE C1 7

U S railroad employees in area II classed by size of community metropolis (population 150 000 to one million) city (50 000 to 150 000) town (less than 50 000) number of men in the roster invited and examined and men examined as % of men invited and in the roster

OCCUPATION	COMMUNITY	ROSTER	INVITED	EXAMINED	RESPONDENTS % OF INVITED	ROSTER
Clerks	Metropolis	572	162	131	81 4	22 9
	City	352	117	99	84 6	28 1
	Town	393	82	61	74 4	15 5
	All	1317	361	291	80 6	22 1
Switchmen	Metropolis	706	230	135	58 7	19 1
	City	362	127	103	81 1	28 5
	Town	368	74	53	71 6	14 4
	All	1436	431	291	67 5	20 6
Executives	Metropolis	271	80	61	76 2	22 5
	City	103	33	25	75 8	24 0
	Town	98	29	21	72 4	21 4
	All	472	142	107	75 4	22 7

6 to 9 years less than those in the other areas The medians were 15 6 17 1 18 5 and 25 5 years in the job for switchmen for ages 40—44 45—49, 50—54 and 55—59 respectively Clerks had substantially fewer years in their present occupations the medians being from 9 to 15 years However these values are biased toward the low side since the questionnaire used did not properly distinguish between changes in jobs within the occupation and changes to jobs outside the occupation Studies of occupation mobility in a 4 per cent sample of all men employed by the railroad industry for ten years or more did show that clerks who were 40—59 at the beginning of the study transferred to jobs outside of the occupation twice as often as the switchmen during a six-year follow-up Retirements withdrawals from the industry and deaths were of the same order of magnitude in the two occupations It is concluded that switchmen remain in their jobs over longer periods of time than clerks

Other Characteristics of the Occupational Samples

Differences in national background, particularly of foreign-born groups, may be associated with different prevalences of risk factors (Epstein *et al* 1957, Stamler *et al* 1960) so nationality of the occupational groups was examined Men brought up in families with both parents of the same national origin were felt to represent potential bias and the analysis centered on this group The data are presented in Table C1 8 Sixty per cent of the clerks reported both parents to be of the same nationality for switchmen and executives the percentages were of the same order of magnitude but slightly lower The distributions of the several national groups in the three occupations had only a few important differences Thirty-six per cent of the clerks had German parents while only 22 per cent of the switchmen and 24 per cent of the executives had German parents Only 1 7 per cent of the executives had parents of Slavic origin while the percentage for clerks was 13 and for switchmen 13 9 The executives also had a larger proportion who stated that their parents were of English-Scottish origin (38 per cent) than the clerks (17 0 per cent) or the switchmen (21 7 per cent) Area differences did not appear to be great except that more than half of all the men of Slavic origin were employed by one Company in Area I

The marital status is presented in Table C1 9 The age-adjusted prevalence of married men among executives was 97 2 per cent for clerks 89 5 and for switchmen 94 1 The major difference between clerks and switchmen was found in the never-married group in which the age-adjusted prevalence was 6 7 per cent in the clerks and 1 8 per cent in the switchmen

Railroad employees as a group are known to have a sub-group of heavy drinkers An estimate of the extent of this behavior was obtained by calculating the age-adjusted prevalence of men who were or had been members of Alcoholics Anonymous The age-adjusted rate in switchmen was 3 9 per cent in clerks 4 2 per cent and zero among executives Presumably alcoholics did not become executives or were eliminated from their jobs or handled their problem in other ways Variability in the area breakdown was not remarkable except that clerks in Area A had a rate of 7 per cent

Switchmen and clerks have approximately the same average rate of pay — 18—19 dollars a day for clerks 21—23 dollars a day for switchmen Switchmen collect more overtime pay but clerks have a better chance of being

TABLE Cl 8

Nationality of the parents of sedentary clerks switchmen and executives Paternal nationality includes all subjects reporting Pure refers to identical paternal and maternal nationality

	Sedentary Clerks			Switchmen			Executives		
	Nationality		Pure	Nationality		Pure	Nationality		Pure
	Paternal	Pure	%	Paternal	Pure	%	Paternal	Pure	%
1 Scandinavian	11 1	15 9	86 6	12 0	16 1	72 8	9 3	13 3	80 0
2 Russian-Polish	9 1	13 0	86 6	8 0	13 9	94 4	1 4	1 7	66 7
3 Hungarian-Rumanian	1 2	1 3	66 7	0 7	1 4	100 0	0 5	0 8	100 0
4 German	33 0	36 0	66 3	23 7	21 8	49 7	26 1	24 2	51 8
5 Italian	2 3	3 6	94 1	2 1	3 3	85 7	2 3	3 3	80 8
6 French Spanish	3 2	1 6	29 1	4 0	1 6	22 2	2 8	2 5	50 0
7 Irish	16 6	11 6	42 3	22 7	19 9	47 4	19 5	15 8	45 2
8 English Scottish	23 5	17 0	43 7	26 8	21 7	44 0	38 1	38 4	56 1
	100 0	100 0		100 0	100 0		100 0	100 0	
N	739	447		679	367		215	120	

TABLE Cl 9

Percentages of married single (never married) widowed divorced and separated men among executives sedentary clerks and switchmen.

	Executives				Sedentary Clerks				Switchmen			
age	40 44	45 49	50 54	55 59	40 44	45 49	50- 54	55 59	40- 44	45- 49	50 54	55- 59
married	100	100	99	90	85	95	89	88	93	93	94	96
single		-	--	5	10	3	7	6	3	2	1	2
widowed		-	1	3	1	1	--	4	--	1	1	1
divorced		--	--	1	3	1	3	2	3	4	3	-
separated	-	-	-	1	1	-	1	--	1	--	1	1
N	46	35	72	95	165	183	237	267	282	242	153	159

promoted to a substantially better paying job Executives, of course have much higher salaries

Distribution of the *Measured Variables*

The personal characteristics related to the development of coronary heart disease found in the several *occupations* are presented in Table CI 10 as the value at the median for the four age groups along with the same figure expressed as per cent of the average of the medians for the 18 population samples covered by the cooperative studies With the exception of both diastolic and systolic blood pressure *all medians for all occupations* are larger than the averages for the groups as a whole In general the American railroad employees were taller heavier for their height fatter and had higher serum cholesterol concentrations than the averages of the medians Clerks and switchmen had comparable heights But the executives were significantly *taller than any of the other occupations* and were the tallest of any group *studied* Switchmen were heavier for height and age at all ages and were thinner in the younger age groups than clerks Executives were as heavy as the switchmen but were also a little fatter In both relative body weight and fatness the employees of the American railroads were *markedly heavier and* fatter than the averages of all groups The men of Crevalcore had relative body weights that were comparable to employees of the American railroads while those of the Italian railroad were larger All occupations had skinfolds which were markedly *larger than in any* other groups studied The blood pressures *in the several* occupations do not show striking trends except that non-sedentary clerks and executives tended to have lower blood pressures in the younger age groups and the non-sedentary clerks were found to have the highest systolic and diastolic blood pressures in the oldest age group Serum cholesterols were markedly elevated above the average for all groups and did not differ significantly between occupations However it should be noted *that the executives tended to have* higher serum cholesterol concentrations *than the other occupational groups* These men had serum cholesterol concentrations which were substantially lower than those of the Finns and were in the same range as those of the men of Zutphen

The relative body weights have a trend to lower values with age in all occupations There is no trend in the *skinfolds* with age The systolic and diastolic blood pressures show the *expected increase with age* Serum cholesterol is not related to age in a uniform way in the four groups Switchmen have an increased serum cholesterol in the 55—59 age group while the other three occupations do not The complete distributions of all the measured *variables are to be found in the* Appendix The data are presented in *Figures CI 1 through CI 4* as cumulative frequency distributions plotted with a probability scale in the ordinate All ages have been pooled for those variables which showed *no age trend* i e height sum of the skinfolds and serum cholesterol concentrations In the *case of the other variables systolic and* diastolic blood pressure and relative body weight the distributions for the age decade 40 to 49 are shown by a heavy line and the 50 to 59 decade is represented by a light line Normal distribution is indicated by a straight *line Examination of the data for seden-*tary clerks and switchmen reveals that the largest departures from normality occur in the blood pressure measurements Serum cholesterol concentration shows a minor bowing *An unusual*

TABLE CI 10

Medians for U S railroad employees and these values expressed as percentages of the average of the medians for all 18 samples of men

VARIABLE	SAMPLE	MEDIAN VALUES				MEDIAN % OF AVERAGE			
		40 44	45 49	50 54	55 59	40 44	45-49	50 54	55 59
Height (cm)									
	Switchmen	175	175	174	172	103 1	103 6	104 0	102 6
	Sed Clerks	175	174	172	172	103 1	103 0	102 8	102 6
	Non-Sed Clerks	173	172	172	173	101 9	101 8	103 4	103 2
	Executives	177	177	177	176	104 2	104 7	105 8	104 9
	All Men	175	174	173	172	103 1	103 0	103 4	102 6
Rel Wt (%)									
	Switchmen	106	103	105	104	108 1	107 1	110 3	110 5
	Sed Clerks	103	102	102	101	105 0	106 0	107 1	107 3
	Non Sed Clerks	104	100	105	101	106 0	104 0	110 3	107 3
	Executives	106	103	103	101	108 1	107 1	108 2	107 3
	All Men	105	103	104	102	107 0	107 1	109 2	108 4
Skinfolds (mm)									
	Switchmen	31	29	33	32	146 2	142 2	159 4	160 8
	Sed Clerks	33	34	33	32	155 7	166 7	159 4	160 8
	Non Sed Clerks	37	34	37	31	174 5	166 7	178 7	155 8
	Executives	33	31	38	34	155 7	152 0	183 6	170 9
	All Men	32	31	34	32	150 9	152 0	164 3	160 8
Syst B P (mm)									
	Switchmen	130	133	136	140	99 2	100 1	99 3	99 6
	Sed Clerks	134	133	142	140	102 3	100 1	103 6	99 6
	Non Sed Clerks	130	133	138	144	99 2	100 1	100 7	102 4
	Executive	123	130	139	133	93 9	97 8	101 5	94 6
	All Men	130	133	139	139	99 2	100 1	101 5	98 9
Diast B P (mm)									
	Switchmen	83	84	85	88	102 5	103 2	101 9	104 4
	Sed Clerks	83	85	88	86	102 5	104 4	105 5	102 0
	Non Sed Clerks	80	80	88	90	98 8	98 3	105 5	106 8
	Executives	80	81	89	85	98 8	99 5	106 7	100 8
	All Men	82	84	87	86	101 2	103 2	104 3	102 0
Serum Chol (mg%)									
	Switchmen	233	232	232	250	112 9	111 9	111 1	120 9
	Sed Clerks	234	234	232	242	113 4	112 9	111 1	117 1
	Non Sed Clerks	228	230	255	221	110 5	111 0	122 1	106 9
	Executives	242	241	243	247	117 2	116 3	116 3	119 5
	All Men	234	234	234	243	113 4	112 9	112 0	117 6

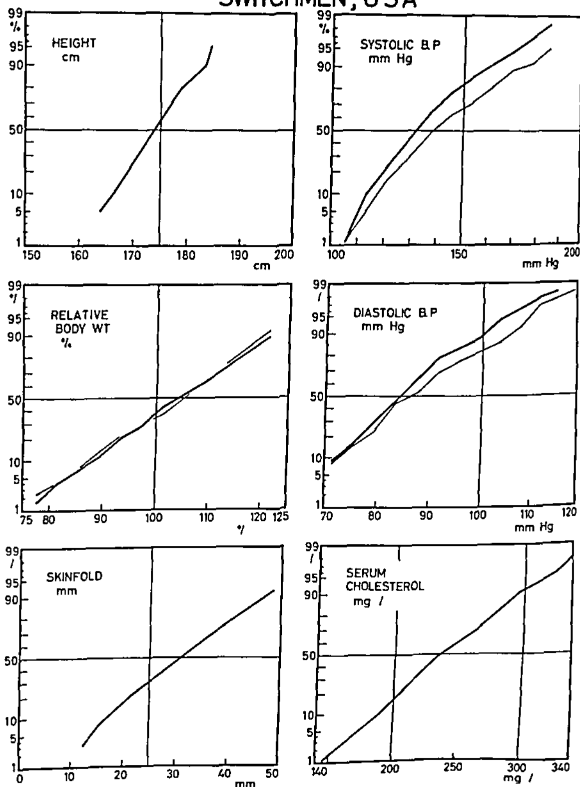

SWITCHMEN, USA
HEIGHT
cm
SYSTOLIC B.P
mm Hg
RELATIVE
BODY WT
%
DIASTOLIC B.P
mm Hg
SKINFOLD
mm
SERUM
CHOLESTEROL
mg /
99
95
90
50
10
5
1
150
160
170
180
190
200
cm
100
150
200
mm Hg
75
80
90
100
110
120
125
%
70
80
90
100
110
120
mm Hg
0
10
20
30
40
50
mm
140
200
250
300
340
mg /

Figure C1 1

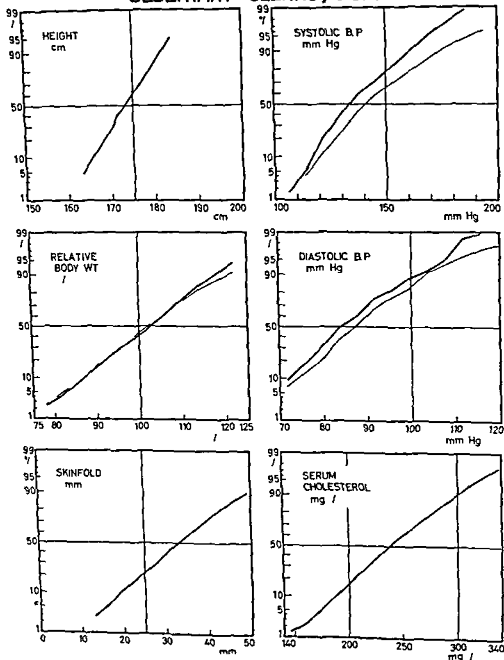

SEDENTARY CLERKS, U.S.A
HEIGHT cm
SYSTOLIC B.P mm Hg
RELATIVE BODY WT
DIASTOLIC B.P mm Hg
SKINFOLD mm
SERUM CHOLESTEROL mg
cm
mm Hg
mm Hg
mm

Figure C1.2

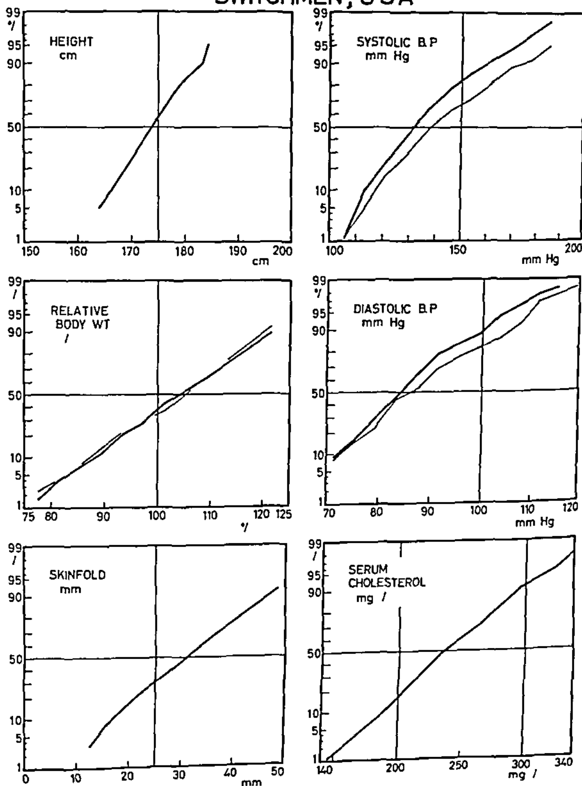

SWITCHMEN, USA
HEIGHT cm
SYSTOLIC B.P mm Hg
RELATIVE BODY WT %
DIASTOLIC B.P mm Hg
SKINFOLD mm
SERUM CHOLESTEROL mg %
99
95
90
50
10
5
1
150 160 170 180 190 200
cm
100 150 200
mm Hg
75 80 90 100 110 120 125
%
70 80 90 100 110 120
mm Hg
0 10 20 30 40 50
mm
140 200 250 300 340
mg %

Figure CI 1

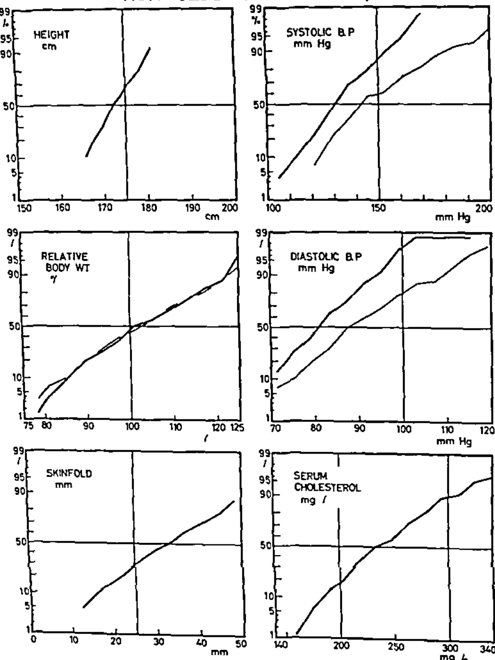

NON-SEDENTARY CLERKS, USA
HEIGHT cm
SYSTOLIC B.P mm Hg
RELATIVE BODY WT %
DIASTOLIC B.P mm Hg
SKINFOLD mm
SERUM CHOLESTEROL mg %

Figure C1 4

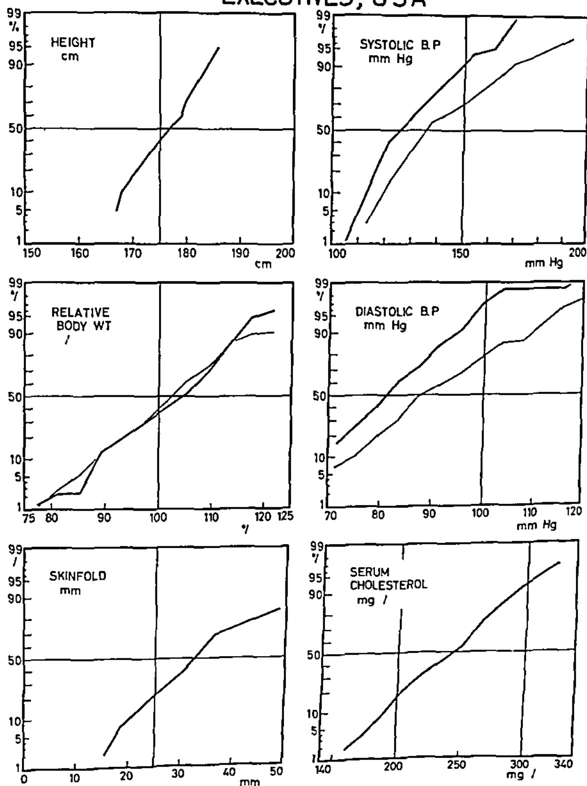

EXECUTIVES, USA
HEIGHT
cm
SYSTOLIC B.P
mm Hg
RELATIVE
BODY WT
%
DIASTOLIC B.P
mm Hg
SKINFOLD
mm
SERUM
CHOLESTEROL
mg %

Figure C1.3

TABLE C1 11

C garette smoking habits of men of the U S Railroad Percentage of men who never smoked who had stopped who smoked 1-10 11 20 more than 20 cigarettes daily at the time of their examination

SAMPLE	AGE	NEVER	QUIT	1-10	11 20	MORE THAN 20
Switchmen	40 44	15 6	13 8	6 7	27 0	36 9
	45 49	15 3	19 4	4 5	32 3	28 5
	50 54	18 8	22 1	6 5	26 0	26 6
	55 59	17 0	23 3	4 4	30 8	24 5
	40 59	16 4	18 8	5 6	29 0	30 2
S dentary Clerks	40 44	25 7	16 8	4 8	38 9	13 8
	45 49	26 5	20 6	4 3	26 4	22 2
	50 54	27 6	20 1	7 1	30 1	15 1
	55 59	28 2	23 8	8 2	23 8	16 0
	40 59	27 2	20 7	6 4	29 1	16 6
Executive	40 44	26 1	17 4		30 4	26 1
	45 49	20 0	20 0	2 9	22 9	34 2
	50 54	26 0	4 7	1 4	17 8	30 1
	55 59	25 8	22 7	6 2	19 6	25 7
	40 59	25 1	21 9	3 2	21 5	28 3
No Sed ntary Cle k	40 44	22 6	19 4	6 5	38 6	12 9
	45 49	[illegible]3 1	15 4	7 7	35 9	17 9
	50 54	21 1	15 8	7 9	39 4	15 8
	55 59	21 3	25 5	17 0	21 3	14 9
	40 59	21 9	19 4	10 3	3[illegible] 9	15 5

finding is the apparently normal distribution for skinfolds among sedentary clerks Switchmen show a minor departure from the straight line and both groups have normal distributions of relative body weights and heights The small numbers of men in the executive and non-sedentary clerks result in less stable graphs The same general picture emerges except for sum of the skinfolds in executives which has a definite bow and irregularities in the graph make it difficult to be sure that relative body weight has a normal distribution in either occupation

Smoking habits of the occupational groups are presented in Table C1 11 A larger fraction of switchmen smoke cigarettes (64 8 %) than clerks (52 1 %) or executives (53 %) There were 30 2 % of switchmen and 28 3 % of executives who smoked more than 20 cigarettes a day while only 16 6 % of the clerks were heavy smokers Relationships between smoking categories and the measured variables in switchmen and clerks are presented in Table C1 12

In non-smokers there was an excess of men observed over that expected above the median value in both occupations for relative body weight (126 % for switchmen and 114 4 % for clerks) and sum of the skinfolds (123 5 % for switchmen and 113 7 % for clerks) The reverse relationship was found in heavy smokers where a smaller fraction of men was observed than expected above the median in both occupations No substantial relationship to smoking was found in either the systolic and diastolic blood pressures or the serum cholesterol concentration

The Electrocardiographic Findings

The ECG findings for the four groups are presented in Tables C1 13 through C1 20 The large Q waves (code I 1) which can be taken as evidence of old myocardial infarction have very low frequencies in all groups and it is not possible to make any statements regarding differences in prevalence rates between groups There were no important differences between clerks and switchmen in all reportable items, clerks had fewer total Q waves in the 40 to 49 decade while the reverse was true in the older decade of age Switchmen had fewer cases of left axis deviation than clerks at all age groups The most striking finding between occupations was found in the S-T depressions after exercise Clerks showed an age-adjusted rate of 67.3 and switchmen of 25 6 The difference is highly significant The number of men in the executive group is too small to draw firm conclusions Age-adjusted rates per 1000 for the men classified as having an "ischemic pattern" (code XI 1—3) were sedentary clerks 29 0 switchmen 15 3 and executives 23 4 For code XI 4 (non-ischemic pattern) the corresponding rates were 38 3 10 3 and 16 6 for sedentary clerks switchmen and executives

Prevalence of Hypertension versus Other Variables

The prevalence of hypertension in switchmen clerks and executives does not differ markedly between occupational classes but is definitely higher than the average prevalence for all samples Table C1 21 presents prevalence rates based on two criteria of blood pressure by age and occupation The age-adjusted rates of hypertension defined as 95 mm Hg or more in the fifth phase of diastole in numbers per thousand are 210 230 273 and 212 for switchmen sedentary clerks non sedentary clerks and executives respectively while the rate for all areas was

TABLE C1 13

SWITCHMEN U S A

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code		AGE GROUP (Number of Men) 40 44 (282)	45 49 (241)	50 54 (153)	55 59 (159)
Total with reportable ECG Items	I IX		56 (198 6)	58 (240 7)	37 (241 8)	45 (283 0)
Q Waves	I	1	3 (10 6)	2 (8 3)	3 (19 6)	0
		2	3 (10 6)	5 (20 7)	3 (19 6)	5 (31 4)
		3	1 (3 5)	5 (20 7)	0	1 (6 3)
Axis Deviation	II					
Left		1	4 (14 2)	3 (12 4)	4 (26 1)	3 (18 9)
Right		2	0	0	0	0
High Amplitude R Waves	III					
Left type		1	1 (3 5)	6 (24 9)	3 (19 6)	3 (18 9)
Right type		2	0	0	0	0
S T Depression (rest)	IV					
S T J 1 mm or more horiz or downward segment		1	0	0	1 (6 5)	0
S T J 0 5 1 mm horiz or downward segment		2	0	0	0	3 (18 9)
No S T J plus segment downward		3	1 (3 5)	2 (8 3)	0	3 (18 9)
S T J 1 mm or more upward segment		4	0	0	0	0
T Wave Negativity (rest)	V					
5 mm or more		1	0	0	0	0
1 mm to 5 mm		2	1 (3 5)	1 (4 1)	1 (6 5)	2 (12 6)
0 ± 1 mm		3	7 (24 8)	5 (20 7)	5 (32 7)	8 (50 3)
A V Conduction Defect	VI					
Complete Block		1	0	0	0	0
Partial Block		2	0	0	0	0
P R over 0 21 second		3	0	0	1 (6 5)	3 (18 9)
Accelerated Conduction		4	2 (7 1)	2 (8 3)	0	0
Ventricular Blocks	VII					
Left Bundle		1	0	0	2 (13 2)	0
Right Bundle		2	0	2 (8 3)	3 (19 9)	3 (18 9)
Incomplete Right Bundle		3	5 (17 7)	1 (4 1)	3 (19 9)	3 (18 9)
Intraventricular Block		4	0	1 (4 1)	0	0
Arrhythmias	VIII					
Premature Beats		1	0	3 (12 4)	0	0
Ventricular tachycardia		2	0	0	0	0
Atrial fibrillation flutter		3	0	0	0	0
Supraventricular tachycardia		4	0	0	0	0
Ventricular rhythm		5	0	0	0	0
A V nodal rhythm		6	0	0	0	0
Sinus tachycardia		7	3 (10 6)	3 (12 4)	0	3 (18 9)
Sinus bradycardia		8	3 (10 6)	1 (4 1)	4 (26 5)	2 (12 6)
Technically poor records	IX	8	0	4 (16 7)	0	0

TABLE CI 12

Smoking Number of men in the U S Railroad below (LOW) and above (HIGH) the age specific medians for age and area, of measured variables classed according to smoking habits HEAVY more than 20, OTHER 1 20 cigarettes daily

VARIABLE	SAMPLE	NON-SMOKERS		HEAVY		OTHER	
		LOW	HIGH	LOW	HIGH	LOW	HIGH
Relative Weight	Switchmen	108	185	136	115	173	116
	Clerks	175	234	75	68	178	126
Σ Skinfolds	Switchmen	112	181	130	122	176	114
	Clerks	177	233	76	67	176	149
Systolic B P	Switchmen	135	159	123	129	160	130
	Clerks	209	202	70	71	151	155
Diastolic B P	Switchmen	135	159	124	128	159	131
	Clerks	206	205	67	74	157	149
Serum Cholesterol	Switchmen	144	145	123	125	145	141
	Clerks	209	199	77	66	141	161

TABLE C1 15

SEDENTARY CLERKS U S A.

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

		AGE GROUP (Number of Men)			
	ECG	40 44	45-49	50-54	55 59
ECG FINDING	Code	(165)	(184)	(234)	(264)
Total with reportable ECG Items	I - IX	28 (169 7)	37 (201, 1)	62 (265 0)	66 (250 0)
Q Waves	I 1	1 (6 1)	2 (10 9)	1 (4 3)	6 (22 7)
	2	1 (6 1)	0	3 (12 8)	5 (18 9)
	3	0	0	1 (4 3)	9 (34 1)
Axis Deviation	II				
Left	1	4 (24 2)	7 (38 0)	8 (34 2)	16 (60 6)
R gnt	2	0	0	0	0
High Amplitude R Waves	III				
L ft type	1	3 (18 2)	4 (21 7)	10 (42 7)	12 (45 5)
Right typ	2	0	0	0	0
S T D pression (rest)	IV				
S T J 1 mm or more horiz or downward segm nt	1	0	0	1 (4 3)	6 (22 7)
S T J 0 5 1 mm horiz or downward segment	2	2 (12 1)	0	6 (25 6)	3 (11 4)
No S T J plus segment downward	3	0	0	2 (8 5)	1 (3 8)
S T J 1 mm or more upward egment	4	0	1 (5 4)	0	1 (3 8)
T Wav Negativity (rest)	V				
5 mm or more	1	0	0	0	1 (3 8)
1 mm to 5 mm	2	2 (12 1)	2 (10 9)	5 (21 4)	7 (26 5)
0 ± 1 mm	3	3 (18 2)	3 (16 3)	4 (17 1)	13 (49 2)
A V Conduction Defect	VI				
Complete Block	1	0	0	0	0
Partial Block	2	0	0	0	0
P R over 0 21 second	3	0	0	1 (4 3)	1 (3 8)
Accele ated Conduction	4	1 (6 1)	0	1 (4 3)	3 (11 4)
Ventricular Blocks	VII				
Left Bundle	1	1 (6 1)	0	6 (25 6)	2 (7 6)
Right Bundle	2	0	0	0	2 (7 6)
Incomplete Right Bundle	3	1 (6 1)	2 (10 9)	1 (4 3)	4 (15 2)
Intrav ntricular Block	4	0	0	0	1 (3 8)
A rhythmias	VIII				
P mature B ats	1	0	2 (10 9)	1 (4 3)	6 (22 7)
V ntricular tachycard a	2	0	0	0	0
Atrial fibrillation flutter	3	0	0	1 (4 3)	3 (11 4)
Sup a vent tachycardia	4	0	0	0	0
V ntricula rhythm	5	0	0	0	0
A V nodal rhythm	6	1 (6 1)	0	0	0
S nus tachycardia	7	4 (24 2)	3 (16 3)	6 (25 6)	10 (37 9)
S us bradyca dia	8	2 (12 1)	1 (5 4)	2 (8 5)	0
Techn cally poor reco ds	IX 8	0	2 (10 9)	2 (8 5)	1 (3 8)

TABLE C1 14

SWITCHMEN U S A

FREQUENCY OF POST EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40 44 (278)	45 49 (233)	50-54 (141)	55 59 (143)
Exercise tests not made or	X 1				
incomplete	X 2	4 (14 2)	8 (33 2)	12 (78 4)	16 (100 6)
S-T Depression post-exercise (none at rest)	XI				
S T - J 1 mm or more horiz or downward segment	1	0	1 (4 2)	0	1 (7 0)
S T - J 0 5 - 1 mm , horiz or downward segment	2	2 (7 1)	5 (21 5)	2 (14 2)	1 (7 0)
No S-T J plus segment downward	3	0	0	0	0
S-T - J 1 mm or more upward segment	4	0	3 (12 9)	2 (14 2)	2 (14 0)
T Wave Negativity post exercise (none at rest)	XII				
-5 mm or more	1	0	0	0	0
-1 to -5 mm	2	0	2 (8 6)	1 (7 1)	0
0 ± 1 mm	3	1 (3 6)	0	0	1 (7 0)
Arrhythmias post-exercise	XV				
(none at rest)	1	0	2 (8 6)	0	1 (7 0)
Technically poor post-exercise records	XI 8	6 (21 6)	5 (21 5)	6 (42 6)	7 (49 0)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

ECG FINDING	ECG Code	40 44	45 49	50-54	55 59
At Rest					
Large Q Waves	I 1	3 (10 6)	2 (8 3)	3 (19 6)	0
Lesser Q Waves with Negative T Waves	I 2 3 + V 1,2	0	0	0	0
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2,3 only	6 (21 3)	2 (8 3)	3 (19 6)	5 (31 4)
S-T Depression as sole anomaly	IV 1-4 only	1 (3 5)	1 (4 1)	0	2 (12 6)
High Amplitude R with S-T Depression	III 1 + IV 1-4	0	0	1 (6 5)	1 (6 3)
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2 4	0	3 (12 4)	5 (32 7)	3 (18 9)
Arrhythmias	VIII 2-6	0	0	0	0
Post exercise					
S T Depression as sole anomaly	XI 1-4 only	2 (7 1)	6 (25 8)	3 (21 3)	3 (21 0)
Negative T as sole anomaly	XII 1-3 only	0	0	0	0
Ventricular Conduction Defect as sole anomaly	XIV 1 2 4 only	0	0	0	0
Arrhythmias as sole anomaly	XV 1 only	0	2 (8 6)	0	1 (7 0)

TABLE C1 15

SEDENTARY CLERKS U S A.

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40 44 (165)	45 49 (184)	50 54 (234)	55 59 (264)
Total with reportable ECG Items	I IX	28 (169 7)	37 (201.1)	62 (265 0)	66 (250 0)
Q Waves	I 1	1 (6 1)	2 (10 9)	1 (4 3)	6 (22 7)
	2	1 (6 1)	0	3 (12 8)	5 (18 9)
	3	0	0	1 (4 3)	9 (34 1)
Axis Deviation	II				
Left	1	4 (24 2)	7 (38 0)	8 (34 2)	16 (60 6)
Right	2	0	0	0	0
High Amplitude R Waves	III				
Left type	1	3 (18 2)	4 (21 7)	10 (42 7)	12 (45 5)
Right type	2	0	0	0	0
S T Depression (rest)	IV				
S T J 1 mm or more horiz or downward segment	1	0	0	1 (4 3)	6 (22 7)
S T J 0 5 1 mm horiz or downward segment	2	2 (12 1)	0	6 (25 6)	3 (11 4)
No S T J plus segment downward	3	0	0	2 (8 5)	1 (3 8)
S T J 1 mm or more upward segment	4	0	1 (5 4)	0	1 (3 8)
T Wave Negativity (rest)	V				
5 mm or more	1	0	0	0	1 (3 8)
1 mm to 5 mm	2	2 (12 1)	2 (10 9)	5 (21 4)	7 (26 5)
0 ± 1 mm	3	3 (18 2)	3 (16 3)	4 (17 1)	13 (49 2)
A V Conduction Defect	VI				
Complete Block	1	0	0	0	0
Partial Block	2	0	0	0	0
P R over 0 21 second	3	0	0	1 (4 3)	1 (3 8)
Accelerated Conduction	4	1 (6 1)	0	1 (4 3)	3 (11 4)
Ventricular Blocks	VII				
Left Bundle	1	1 (6 1)	0	6 (25 6)	2 (7 6)
Right Bundle	2	0	0	0	2 (7 6)
Incomplete Right Bundle	3	1 (6 1)	2 (10 9)	1 (4 3)	4 (15 2)
Intraventricular Block	4	0	0	0	1 (3 8)
Arrhythmias	VIII				
Premature Beats	1	0	2 (10 9)	1 (4 3)	6 (22 7)
Ventricular tachycardia	2	0	0	0	0
Atrial fibrillation flutter	3	0	0	1 (4 3)	3 (11 4)
Supraventricular tachycardia	4	0	0	0	0
Ventricular rhythm	5	0	0	0	0
A V nodal rhythm	6	1 (6 1)	0	0	0
Sinus tachycardia	7	4 (24 2)	3 (16 3)	6 (25 6)	10 (37 9)
Sinus bradycardia	8	2 (12 1)	1 (5 4)	2 (8 5)	0
Technically poor records	IX 8	0	2 (10 9)	2 (8 5)	1 (3 8)

TABLE CI 14

SWITCHMEN U S A

FREQUENCY OF POST-EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1,000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40 44 (278)	45-49 (233)	50-54 (141)	55 59 (143)
Exercise tests not made or incomplete	X 1 X 2	4 (14 2)	8 (33 2)	12 (78 4)	16 (100 6)
S-T Depression post-exercise (none at rest)	XI				
S-T - J 1 mm or more, horiz or downward segment	1	0	1 (4 2)	0	1 (7 0)
S-T - J 0 5 - 1 mm , horiz or downward segment	2	2 (7 1)	5 (21 5)	2 (14 2)	1 (7 0)
No S-T-J plus segment downward	3	0	0	0	0
S-T - J 1 mm or more upward segment	4	0	3 (12 9)	2 (14 2)	2 (14 0)
T Wave Negativity post-exercise (none at rest)	XII				
-5 mm or more	1	0	0	0	0
-1 to 5 mm	2	0	2 (8 6)	1 (7 1)	0
0 ± 1 mm	3	1 (3 6)	0	0	1 (7 0)
Arrhythmias post-exercise (none at rest)	XV 1	0	2 (8 6)	0	1 (7 0)
Technically poor post-exercise records	XI 8	6 (21 6)	5 (21 5)	6 (42 6)	7 (49 0)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

At Rest					
Large Q Waves	I 1	3 (10 6)	2 (8 3)	3 (19 6)	0
Lesser Q Waves with Negative T Waves	I 2 3 + V 1, 2	0	0	0	0
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	6 (21 3)	2 (8 3)	3 (19 6)	5 (31 4)
S-T Depression as sole anomaly	IV 1-4 only	1 (3 5)	1 (4 1)	0	2 (12 6)
High Amplitude R with S-T Depression	III 1 + IV 1-4	0	0	1 (6 5) 0	1 (6 3) 0
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2 4	0	3 (12 4)	5 (32 7)	3 (18 9)
Arrhythmias	VIII 2-6	0	0	0	0
Post-exercise					
S-T Depression as sole anomaly	XI 1-4 only	2 (7 1)	6 (25 8)	3 (21 3)	3 (21 0)
Negative T as sole anomaly	XII 1-3 only	0	0	0	0
Ventricular Conduction Defect as sole anomaly	XIV 1 2 4 only	0	0	0	0
Arrhythmias as sole anomaly	XV 1 only	0	2 (8 6)	0	1 (7 0)

TABLE C1 17

EXECUTIVES U S A

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code		AGE GROUP (Number of Men) 40 44 (46)	45 49 (35)	50 54 (73)	55 59 (96)
Total with reportable ECG Items	I IX		6 (130 4)	8 (228 6)	23 (315 1)	33 (343 8)
Q Waves	I	1	1 (21 7)	1 (28 6)	1 (13 7)	1 (10 4)
		2	0	1 (28 6)	4 (54 8)	4 (41 7)
		3	0	0	2 (27 4)	0
Axis Deviation	II					
Left		1	1 (21 7)	0	3 (41 1)	6 (62 5)
Right		2	0	0	0	0
High Amplitude R Waves	III					
Left type		1	0	0	1 (13 7)	2 (20 8)
Right type		2	0	1 (28 6)	0	0
S T D pression (rest)	IV					
S T J 1 mm or mor ho iz or downward segment		1	0	1 (28 6)	0	0
S T J 0 5 1 mm horiz or downward segment		2	0	0	1 (13 7)	0
No S T J plus segment downward		3	0	0	1 (13 7)	3 (31 2)
S T J 1 mm or more upward egment		4	0	0	1 (13 7)	0
T Wave Negativity (rest)	V					
5 mm or more		1	0	1 (28 6)	0	0
1 mm to 5 mm		2	0	0	1 (13 7)	1 (10 4)
0 ± 1 mm		3	1 (21 7)	0	3 (41 1)	4 (41 7)
A V Conduction Defect	VI					
Complete Block		1	0	0	0	0
Partial Block		2	0	0	0	0
P R over 0 21 second		3	0	0	0	0
A c l ated Conduction		4	0	0	0	0
V nt cular Blocks	VII					
L ft Bundle		1	0	0	0	1 (10 4)
Right Bundl		2	0	0	1 (13 7)	2 (20 8)
Incompl t Right Bundle		3	0	0	2 (27 4)	1 (10 4)
Int av nt icular Block		4	0	0	1 (13 7)	2 (20 8)
Ar hythmi	VIII					
Pr m tu e B ats		1	0	0	0	3 (31 2)
V nt i ula t chycardia		2	0	0	0	0
Atrial f br llation flutt		3	0	0	0	0
S pra vent tachycardia		4	0	0	0	0
V tricular rhythm		5	0	0	0	0
A V nodal rhythm		6	0	0	0	0
S u ta hy a d a		7	0	0	2 (27 4)	1 (10 4)
S b adycard a		8	0	1 (28 6)	0	2 (20 8)
lly poo ord	IX	8	0	1 (28 6)	0	1 (10 4)

TABLE CI 16

SEDENTARY CLERKS, U S A

FREQUENCY OF POST-EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1,000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (159)	45-49 (176)	50-54 (209)	55-59 (219)
Exercise tests not made or	*X 1*				
incomplete	X 2	6 (36 4)	8 (43 5)	25 (106 8)	45 (170 5)
S-T Depression post-exercise (none at rest)	XI				
S-T - J 1 mm or more horiz or downward segment	1	0	2 (11 4)	2 (9 6)	4 (18 3)
S-T - J 0 5 - 1 mm , horiz or downward segment	2	1 (6 3)	3 (17 0)	1 (4 8)	7 (32 0)
No S-T-J plus segment downward	*3*	*1 (6 3)*	*1 (5 7)*	*0*	*1 (4 6)*
S T - J 1 mm or more upward segment	4	5 (31 4)	5 (28 4)	9 (43 1)	11 (50 2)
T Wave Negativity post exercise (none at rest)	XII				
-5 mm or more	1	0	0	0	0
-1 to -5 mm	2	0	2 (11 4)	1 (4 8)	2 (9 1)
0 ± 1 mm	3	1 (6 3)	2 (11 4)	1 (4 8)	5 (22 8)
Arrhythmias post-exercise	XV				
(none at rest)	1	0	2 (11 4)	0	1 (4 6)
Technically poor post-exercise records	XI 8	5 (31 4)	11 (62 5)	7 (33 5)	12 (54 8)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

ECG FINDING	ECG Code	40-44 (159)	45-49 (176)	50-54 (209)	55-59 (219)
At Rest					
Large Q Waves	I 1	1 (6 1)	2 (10 9)	1 (4 3)	6 (22 7)
Lesser Q Waves with Negative T Waves	*I 2 3 +* V 1, 2	0	0	0	1 (3 8)
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	3 (18 2)	5 (27 2)	2 (8 5)	5 (18 9)
S T *Depression* as sole anomaly	IV 1-4 only	0	1 (5 4)	4 (17 1)	1 (3 8)
High Amplitude R with S-T Depression	III 1 + IV 1-4	0	0	1 (4 3)	3 (11 4)
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1, 2 4	1 (6 1)	0	6 (25 6)	5 (18 9)
Arrhythmias	VIII 2 6	1 (6 1)	0	1 (4 3)	3 (11 4)
Post-exercise					
S-T Depression as sole anomaly	XI 1-4 only	6 (37 7)	6 (34 1)	11 (52 6)	13 (59 4)
Negative T as sole anomaly	XII 1-3 only	1 (6 3)	2 (11 4)	3 (14 4)	6 (27 4)
Ventricular Conduction Defect as sole anomaly	XIV 1 2 4 only	0	0	*0*	*0*
Arrhythmias as sole anomaly	XV 1 only	*0*	1 (5 7)	2 (9 6)	2 (9 1)

TABLE C1 19

NON SEDENTARY CLERKS U S A.

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

		AGE GROUP (Number of Men)			
ECG FINDING	ECG Code	40 44 (32)	45-49 (39)	50 54 (38)	55 59 (46)
Total with reportable ECG Items	I IX	10 (312 5)	9 (230 8)	14 (368 4)	23 (500 0)
Q Waves	I 1	0	1 (25 6)	1 (26 3)	0
	2	1 (31 2)	0	1 (26 3)	1 (21 7)
	3	1 (31 2)	0	2 (52 6)	0
Axis Deviation	II				
Left	1	0	1 (25 6)	1 (26 3)	3 (65 2)
Right	2	0	0	0	0
High Amplitude R Waves	III				
Left type	1	2 (62 5)	2 (51 3)	3 (78 9)	3 (65 2)
Right type	2	0	0	0	0
S T D pression (rest)	IV				
S T J 1 mm or more horiz or downward segment	1	1 (31 2)	0	0	0
S T J 0 5 1 mm horiz or downward segment	2	0	0	0	2 (43 5)
No S T J plus segment downward	3	0	0	1 (26 3)	1 (21 7)
S T J 1 mm or more upward segment	4	0	0	0	0
T Wave Negativity (rest)	V				
5 mm or more	1	0	0	0	1 (21 7)
1 mm to 5 mm	2	2 (62 5)	0	1 (26 3)	1 (21 7)
0 ± 1 mm	3	0	0	2 (52 6)	0
A V Conduction Defect	VI				
Complete Block	1	0	0	0	0
Partial Block	2	0	0	0	0
P R over 0 21 second	3	0	1 (25 6)	1 (26 3)	1 (21 7)
Ac elerated Conduction	4	0	0	0	0
V ntricular Blocks	VII				
Left Bundle	1	0	0	0	0
Right Bundle	2	0	0	0	4 (87 0)
Incomplete Right Bundle	3	1 (31 2)	0	1 (26 3)	0
Int a entricular Block	4	0	1 (25 6)	2 (52 6)	0
Arrhythmias	VIII				
P m tu e Beats	1	0	0	0	3 (65 2)
Vent icular tachycardia	2	0	0	0	0
Atrial fibrillation flutte	3	0	0	0	1 (21 7)
Supra vent tachycardia	4	0	0	0	0
Vent icula hythm	5	0	0	0	0
A V nodal rhythm	6	0	0	0	0
S nu tachy ardia	7	1 (31 2)	0	2 (52 6)	1 (21 7)
Si us bradycardia	8	1 (31 2)	0	0	0
T chn cally poor records	IX 8	1 (31 2)	0	0	1 (21 7)

TABLE C1 18

EXECUTIVES U S A.

FREQUENCY OF POST-EXERCISE ELECTROCARDIOGRAPHIC FINDINGS

(Rate per 1,000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (45)	45-49 (33)	50 54 (68)	55 59 (81)
Exercise tests not made or	X 1				
incomplete	X 2	1 (21 7)	2 (57 1)	5 (68 5)	15 (156 2)
S-T Depression post-exercise (none at rest)	XI				
S-T - J 1 mm or more horiz or downward segment	1	0	0	2 (29 4)	2 (24 7)
S-T - J 0 5 - 1 mm , horiz or downward segment	2	0	0	1 (14 7)	2 (24 7)
No S-T-J plus segment downward	3	0	0	0	0
S-T - J 1 mm or more upward segment	4	0	0	2 (29 4)	3 (37 0)
T Wave Negativity post-exercise (none at rest)	XII				
-5 mm or more	1	0	0	0	1 (12 3)
-1 to -5 mm	2	0	0	0	1 (12 3)
0 ± 1 mm	3	0	0	1 (14 7)	1 (12 3)
Arrhythmias post-exercise	XV				
(none at rest)	1	0	0	0	1 (12 3)
Technically poor post-exercise records	XI 8	0	2 (60 6)	1 (14 7)	4 (49 4)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

ECG FINDING	ECG Code	40-44 (45)	45-49 (33)	50 54 (68)	55 59 (81)
At Rest					
Large Q Waves	I 1	1 (21 7)	1 (28 6)	1 (13 7)	1 (10 4)
Lesser Q Waves with Negative T Waves	I 2 3 + V 1 2	0	0	0	1 (10 4)
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	1 (21 7)	0	0	1 (10 4)
S-T Depression as sole anomaly	IV 1-4 only	0	0	0	1 (10 4)
High Amplitude R with S-T Depression	III 1 + IV 1-4	0	0	1 (13 7)	0
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1, 2, 4	0	0	2 (27 4)	5 (52 1)
Arrhythmias	VIII 2-6	0	0	0	0
Post exercise					
S T Depression as sole anomaly	XI 1-4 only	0	0	3 (44 1)	5 (61 7)
Negative T as sole anomaly	XII 1-3 only	0	0	0	2 (24 7)
Ventricular Conduction Defect as sole anomaly	XIV 1, 2 4 only	0	0	0	2 (24 7)
Arrhythmias as sole anomaly	XV 1 only	0	0	0	0

TABLE Cl 21

Prevalence of diastolic hypertension (95 or more, 100 or more mm Hg fifth phase) among men classed by age Percentage of U S railway men who are hypertensive compared with the average for all 18 samples of men.

SAMPLF	40-44		45-49		50-54		55-59	
	95 mm	100 mm	95 mm	100 mm	95 mm	100 mm	95 mm	100 mm
U S. Switchmen	14.2	9 6	20 6	14.0	22.2	15 0	27 0	20 8
U. S. Sedentary clerks	19 8	12 6	21 2	12 0	26 4	17 6	24.6	17 5
U S. Non-	9 7	3 2	17 9	5 1	36 8	28 9	44 7	27 7
U S. Executives	13 0	8 7	8 6	5 7	42 3	28 2	21 1	13 7
Mean 18 samples	13 6	7 9	15 6	8 9	20 9	13 5	21 5	13 8

TABLE Cl 22

Prevalence of overweight (110 or more and 120 or more per cent of standard average for height and age). Percentage of U S. railway men classed by age who are overweight compared with the average for all 18 samples of men.

SAMPLE	40-44		45-49		50-54		55-59	
	110%	120%	110%	120%	110%	120%	110%	120%
U S. Switchmen	39 9	15 0	31 8	11 7	38 0	9 3	36 1	11 0
U. S. Sedentary clerks	28 8	9 2	22 1	6 6	29 9	10 7	24 5	10 3
U S. Non-	38.7	29 0	28 2	5 1	34 2	18 4	29 8	17 0
U S. Executives	32 6	4 3	22 9	2.9	31 6	8 2	20 6	8 2
Mean 18 samples	20 9	8 4	19 4	6 9	18 1	6 7	16 8	7 3

TABLE CI 20

NON-SEDENTARY CLERKS, U S A

FREQUENCY OF POST-EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1,000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (30)	45-49 (38)	50-54 (30)	55 59 (41)
Exercise tests not made or	X 1				
incomplete	X 2	2 (62 5)	1 (25 6)	8 (210 5)	5 (108 7)
S-T Depression post-exercise (none at rest)	XI				
S-T - J 1 mm or more horiz or downward segment	1	0	0	1 (33 3)	2 (48 8)
S-T - J 0 5 - 1 mm, horiz or *downward segment*	2	2 (66 7)	0	2 (66 7)	1 (24 4)
No S-T-J plus segment downward	3	0	0	0	0
S-T - J 1 mm or more, upward segment	4	0	2 (52 6)	1 (33 3)	0
T Wave Negativity post-exercise (none at rest)	XII				
-5 mm or more	1	0	0	1 (33 3)	0
-1 to -5 mm	2	0	0	0	1 (24 4)
0 + 1 mm	3	0	0	0	0
Arrhythmias post-exercise (none at rest)	XV 1	0	0	1 (33 3)	2 (48 8)
Technically poor post-exercise records	XI 8	1 (33 3)	1 (26 3)	2 (66 7)	1 (24 4)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

At Rest					
Large Q Waves	I 1	0	1 (25 6)	1 (26 3)	0
Lesser Q Waves with Negative T Waves	I 2 3 + V 1 2	2 (62 5)	0	0	0
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2,3 only	0	0	1 (26 3)	0
S-T Depression as sole anomaly	IV 1-4 only	0	0	0	2 (43 5)
High Amplitude R *with S-T Depression*	III 1 + IV 1-4	0	0	0	1 (21 4)
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2 4	0	1 (25 6)	2 (52 6)	4 (87 0)
Arrhythmias	VIII 2 6	0	0	0	1 (21 4)
Post-exercise					
S-T Depression as sole *anomaly*	XI 1-4 only	1 (33 3)	1 (26 3)	1 (33 3)	2 (48 8)
Negative T as sole anomaly	XII 1-3 only	1 (33 3)	2 (52 6)	3 (100 0)	6 (146 3)
Ventricular Conduction Defect as sole anomaly	XIV 1 2 4 only	0	0	0	0
Arrhythmias as sole anomaly	*XV 1* only	0	1 (26 3)	2 (66 7)	2 (48 8)

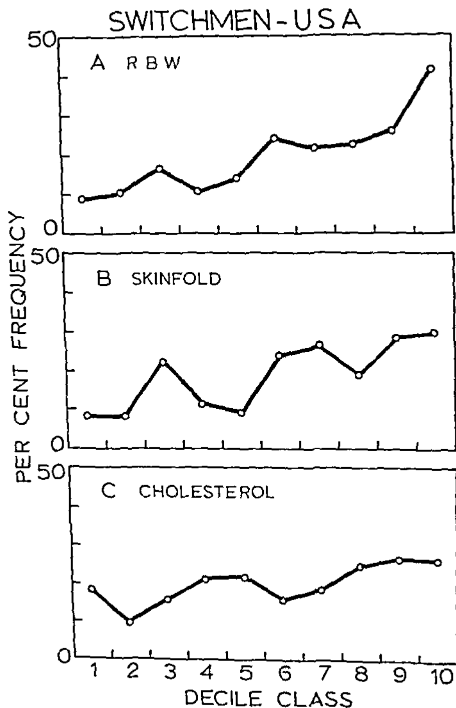

SWITCHMEN - USA
50
A RBW
0
50
B SKINFOLD
0
50
C CHOLESTEROL
0
PER CENT FREQUENCY
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

Figure C1 5

179 Details of the comparisons between occupations will be presented below

The distribution of hypertensive switchmen sedentary clerks and executives (95 mm or more in the fifth phase of diastole) into age specific decile classes of relative body weight Σ skinfolds and serum cholesterol concentrations are presented in Figures C1 5 C1 6 and C1 7 Distributions were prepared for non-sedentary clerks but the small numbers resulted in highly variable prevalence rates in the decile groups For this reason the non-sedentary clerks have been omitted from the analysis If one considers the lower 20 % and the upper 20 % of the relative body weight distribution the per cent frequencies show 3 3 3 2 and 2 7 fold increases for switchmen clerks and executives respectively These are all highly significant increases of the prevalence of hypertension with increasing relative body weight Chisquare values are for switchmen (25 33) sedentary clerks (28 06) and executives (4 72) However, the rise of prevalence of hypertension with increasing obesity as measured by the sum of the skinfolds was significant for switchmen (chi-square 22 63) and sedentary clerks (chi-square 14 21) but not for executives The prevalence of hypertension increased with increasing serum cholesterol only in switchmen where the chi-square was highly significant (chi-square 7 49 p<0 01) In executives there was a definite trend toward more frequent hypertension among men with high serum cholesterol concentration but the significance is doubtful (chi-square 2 56 p>0 10) Since there is no difference between sedentary clerks and switchmen (Table C1 28) or sedentary clerks and executives (Table C1 29) and there is no age trend in serum cholesterol concentration it would appear to be permissible to pool all occupations When this is done it is found that the men in the upper 20 % of the cholesterol concentration distributions have 69 % more cases of hypertension than those in the lower 20 %, and this is highly significant (chi-square 12 23 p<0 0005)

Overweight vs Other Variables

The prevalence of overweight as defined by 110 % or more and 120 % or more of expected weight for height and age is presented in Table C1 22 for the four occupations by five year age groups The average prevalence rate for the 18 samples is included for purposes of comparison

Overweight (relative body weight of 110 % or more) was most common (36 5 %) among switchmen and least common among sedentary clerks (26.3 %) Executives (26 9 %) did not differ from the sedentary or the non-sedentary clerks (32 7 %) By this criterion the tendency of the switchmen to be heavier than the sedentary clerks is statistically highly significant The prevalence of overweight in non-sedentary clerks tends to be greater than in sedentary clerks but the statistical significance is doubtful

The prevalences of overweight (defined as a relative body weight of 110 % or more) by deciles of the other variables are presented in Figures C1 8 C1 9 and C1 10 Inspection of the figures reveals that the prevalence of overweight tends to increase with increasing systolic and diastolic blood pressure for all occupations Chi-square tests of the difference in prevalence found in the lower two deciles and the upper two show the increase in prevalence of overweight among switchmen is highly significant with increasing systolic blood pressure (chi-square 33 15) and diastolic blood pressure (chi-square 17 84) Similar values were found for sedentary clerks (systolic blood pressure chi-square 21 58

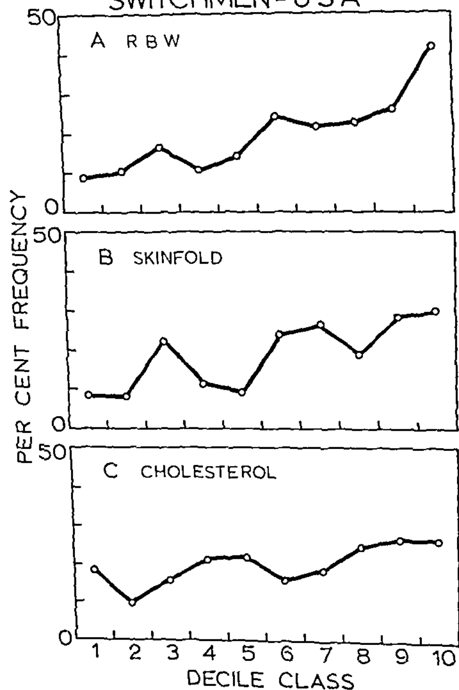
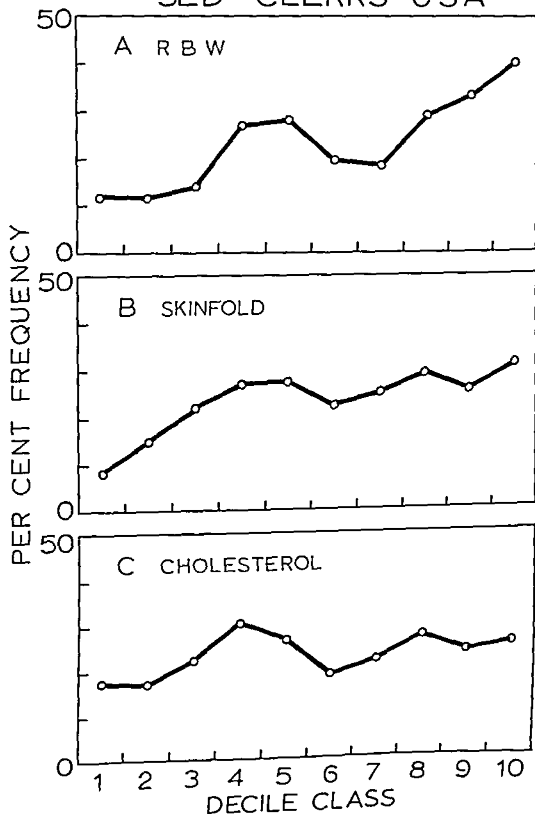

SWITCHMEN - USA
A RBW
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

Figure C.1 5



SED-CLERKS USA
A RBW
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
50
0
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

Figure C1 6

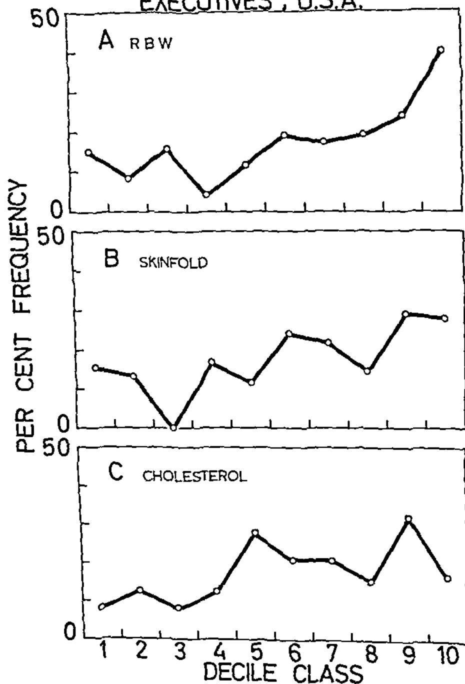
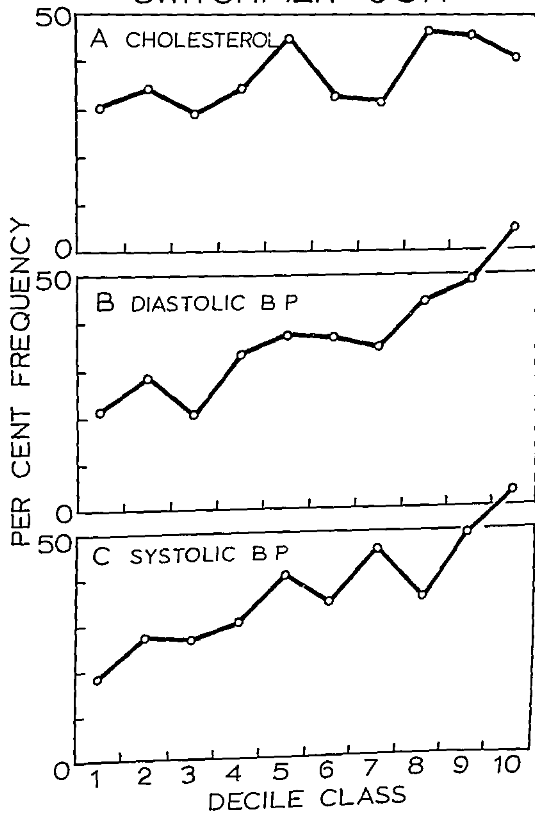

EXECUTIVES, U.S.A.
A RBW
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

Figure C1 7


SWITCHMEN - USA
50
A CHOLESTEROL
0
50
B DIASTOLIC B P
0
50
C SYSTOLIC B P
0
PER CENT FREQUENCY
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

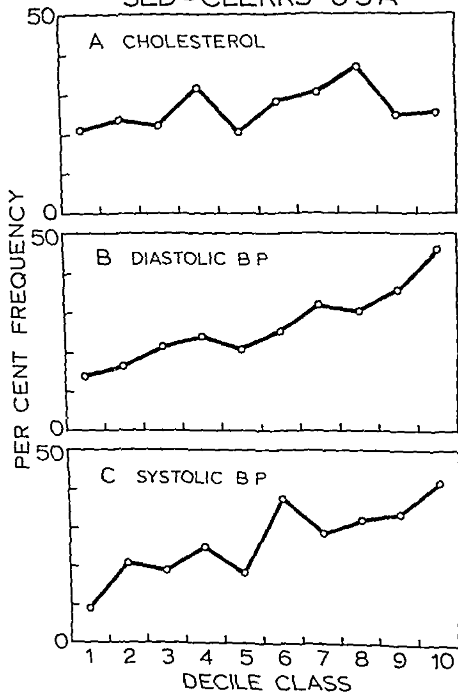

SED-CLERKS USA
A CHOLESTEROL
B DIASTOLIC B P
C SYSTOLIC B P
PER CENT FREQUENCY
50
0
50
0
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

Figure C1 9

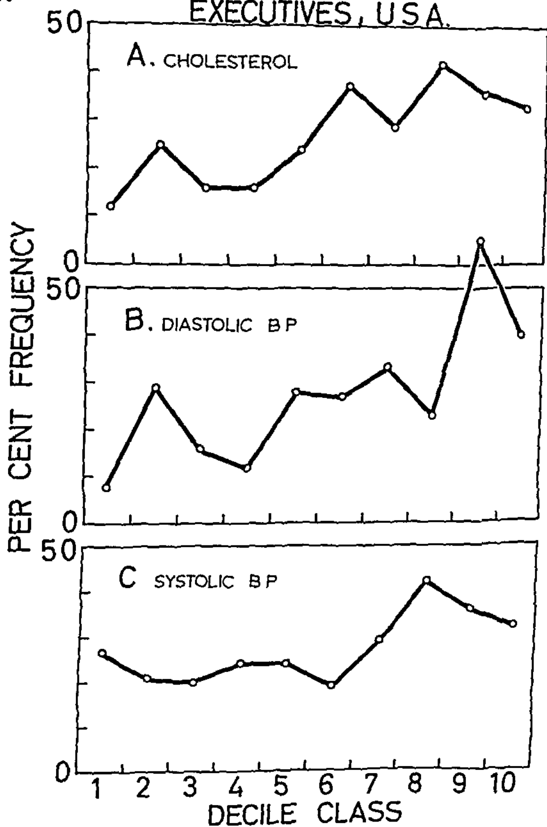

EXECUTIVES, USA.
A. CHOLESTEROL
B. DIASTOLIC BP
C SYSTOLIC BP
PER CENT FREQUENCY
50
0
50
0
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

Figure C1 10

diastolic blood pressure chi square 26 72) but in the executives the prevalence of overweight shows a significant increase from the low to the high end of the distribution only in diastolic pressure (chi square 10 03) On the other hand the only increase in overweight with increasing cholesterol concentration in any of the occupations which approached statistical significance was found in the switchmen (chi-square 3 73 p>0 05)

Differences in Measured Variables between Areas within Occupations

The men in this study were examined at 27 separate locations Five locations were in the Milwaukee-Chicago area (I) and include yards and offices that are located in the suburbs of Chicago Area II included 13 locations Four locations were visited in area III and three in area IV The small numbers of locations in these areas reflect the low population density and the practice of railroad management to concentrate operations in widely separated division points in the Rocky Mountains and in the few large population centers of the West Coast These locations are found in geographical areas differing substantially in the incidence of death from arteriosclerotic heart disease among middle-aged males Such death rates (per year per 100 000) are highest in area IV (594.3) and lowest in area III (440 8) with areas I (535 2) and II (520 1) intermediate (Enterline and Stewart 1956) It seemed worthwhile then to examine the differences in the distributions of the personal characteristics related to the development of heart disease in the several geographic areas In addition urban centers were visited in area II whose population was in the order of magnitude of 1 000 000 and towns whose population was less than 50 000 along with communities of intermediate size

Since the mode of living of a clerk holding a sedentary job in Olewein Iowa (population 8 000 in 1957) is clearly quite different from a clerk holding a comparable job in a general office and commuting to work in Chicago or driving to work in heavy traffic in Minneapolis-St Paul the distribution of the measured variables in cities of different sizes has been examined to identify differences of consequence In area II-B there were five locations whose populations were in the range 500 000 to 1 000 000 population There were two locations in area II-C whose population was in the range of 50 000 to 500 000 and five in area II-C whose populations were less than 50 000

To provide a guide to the absolute levels of the measured variables in several areas the averages of the medians of the four age groups in the geographic areas of switchmen and clerks are presented in Table CI 23 Comparable data for cities and towns in area I and II are presented in Table CI 24 The executives are not included in this analysis because of their high inter-area mobility A more precise and detailed analysis of the differences between areas is given in Table CI 25 For each occupation within a geographic area the number of men whose value of a variable was above the median for occupation and age was determined This number is expressed in the body of the table as a ratio to the number expected (50%) and a similar ratio was computed for men found above the 80th percentile Chi squares were calculated and are shown where the probability of a chance occurrence is small enough to make it worthwhile The clerks showed very few important differences However fewer clerks on the West Coast had skinfold thickness that were above the median for all clerks Similar data were

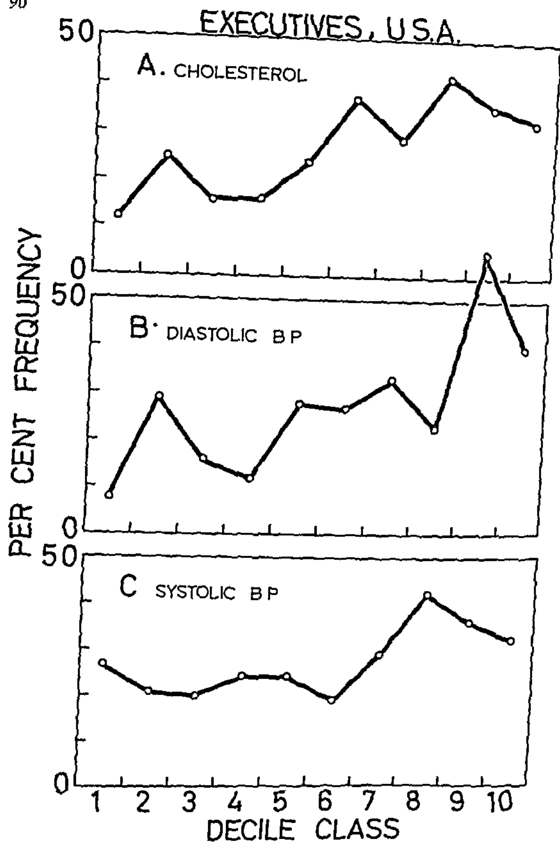

EXECUTIVES, U.S.A.
A. CHOLESTEROL
B. DIASTOLIC B P
C SYSTOLIC B P
PER CENT FREQUENCY
50
0
50
0
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

Figure CI 10

TABLE Cl 25

The ratio of numbers of sedentary clerks or switchmen observed in each area to the number expected above the age specific median and 80th percentile as determined for all men for each of five variables Numbers expected based on distribution of men in all areas The chi square values are given in parentheses Definition of areas are presented in Table Cl 2.

Occupation	Area	Relative Weight	Sum of Skinfolds	Blood Pressure Systolic	Blood Pressure Diastolic	Serum Cholesterol
Switchmen						
Median	I	1 23 (18 91)	1 12 (5 20)	1 10	1 17	1 05
	II	1 06	1 06	1 06	1 09	0 96
	III	0 65 (13 27)	0 69 (10 66)	0 73 (8 62)	0 79 (5 33)	0 94
	IV	0 74 (12 53)	0 89	0 93	0 93 (14 76)	1 05
80th Percentile	I	1 30 (7 08)	1 36 (10 57)	1 30 (6 94)	1 24 (4 28)	1 12
	II	1 20	1 15	0 92	1 05	1 03
	III	0 62	0 57 (4 87)	0 71	0 62 (3 83)	0 76
	IV	0 76	0 45 (14 36)	0 91	0 82	0 91
Sedentary Cl rks						
Median	I	0 98	1 05	1 00	0 93	0 99
	II	1 04	1 04	1 05	1 03	0 97
	III	1 11	1 19	0 81	0 85	1 15
	IV	0 89	0 81 (8 17)	0 94	1 04	1 01
80th Percentile	I	1 02	1 17	1 04	0 85	1 00
	II	1 04	1 01	1 13	1 20	1 06
	III	1 11	1 38	0 37 (5 03)	0 65	0 93
	IV	0 81	0 61 (7 77)	0 92	0 94	0 92

TABLE CI 23

Averages of medians of age groups of the measured variables for sedentary clerks and switchmen in the geographical areas Refer to Table CI 2 for definition of areas

Occupation	Area	Relative Weight (per cent)	Sum of skinfolds (mm)	Blood Pressure Systolic (mm. Hg)	Blood Pressure Diastolic (mm. Hg)	Serum Cholesterol (mg. %)
Sedentary Clerks	I	101.8	33 8	137.4	88 8	233
	II	102.2	33 1	135 9	86 6	235
	III	102 9	35 0	132 6	86 8	244
	IV	101 2	29 6	136 4	90 0	236
Switchmen	I	108 8	33 1	138 9	88 8	241
	II	105 7	31 5	136 2	86 0	236
	III	99 2	27 0	130 4	84 6	235
	IV	101 4	29 6	133 6	86 5	241

TABLE CI 24

Averages of medians of age groups of the measured variables for sedentary clerks and switchmen in area I and II broken down into size of city as follows area I (Chicago-Milwaukee) area II-B (cities with populations of 150 000 to 1 000 000), area II-C (cities with populations of 50,000 to 150 000) and II-D (cities with population of less than 50 000).

Occupation	Area	Relative Weight (per cent)	Sum of Skinfolds (mm)	Blood Pressure Systolic (mm. Hg)	Blood Pressure Diastolic (mm. Hg)	Serum Cholesterol (mg %)
Sedentary Clerks	I	101 8	33 8	137 4	88 8	233
	II-B	104 2	32 6	140 9	89 9	243
	II-C	102 0	34 2	136 8	85 6	225
	II-D	97 8	32 0	132 8	84 8	244
Switchmen	I	108 8	33 1	138 9	88 8	241
	II-B	105 9	32 5	135 6	87 6	234
	II-C	105 9	33 5	135 0	88 8	233
	II-D	104 7	31 2	135 6	86 1	241

TABLE C1 26

The ratio of numbers of sedentary clerks or switchmen observed to the number expected above the age and occupation specific medians and 80th percentiles of all men for each of five variables Areas I and (by size of city) II Numbers expected based on distribution of men in all areas Definitions of areas and city sizes are presented in Table C1 2

		Relative Body Weight	Sum of Skinfolds	Blood Pressure Systolic	Blood Pressure Diastolic	Serum Chol
Occupation	Area	Ratios Based on Median				
Sed Clerks	I	0 96	0 99	1 00	0 98	0 99
	II B	1 12	0 94	1 09	1 16	1 18
	II C	1 21	1 13	0 98	0 94	0 69
	II D	0 87	0 94	0 90	0 86	1 13
Switchmen	I	1 14	1 02	1 02	1 03	1 05
	II B	0 94	1 00	1 03	0 93	0 96
	II C	0 94	1 02	0 94	1 01	0 99
	II D	0 97	0 86	0 96	1 00	0 92
		Ratios Based on 80th Percentile				
Sed Clerks	I	0 95	1 10	0 97	0 85	0 92
	II B	0 93	0 78	1 18	1 31	1 11
	II C	1 03	1 00	0 85	0 91	0 86
	II D	0 85	1 08	1 00	1 17	1 31
Switchmen	I	1 13	1 07	1 17	1 07	1 04
	II B	1 77	0 85	0 97	0 94	0 97
	II C	1 07	1 08	0 78	1 01	0 88
	II D	0 83	0 92	0 67	0 83	1 18

obtained when the 80th percentile for all clerks was applied to those on the West Coast In area I, switchmen were found in larger numbers than expected above the median and also above *the 80th percentile* when the values *for both relative body* weight and the sum of the skinfolds were examined In the Rocky Mountains the switchmen were thinner and therefore a significant *deficit in numbers* was found above both criteria for the sum of the skinfolds Also there were fewer switchmen with relative body weights above the median At the 80th percentile *only 62 % of the expected number* with relative body weights above this cutting point were found but the difference failed to reach significance because of the small numbers involved The blood pressures of switchmen in area III were lower than in the other areas In this area, significantly fewer men than expected were found above the median value for systolic and diastolic blood pressures but only the diastolic blood pressure showed a significantly lower rate above the 80th percentile In area I switchmen had an excess *of men* with blood pressures above the age and occupation specific 80th percentile Finally switchmen on the West Coast had fewer men than expected with diastolic blood pressures above the median

Comparisons between size of cities and towns showed no differences in the distribution of the measured variables except for an apparently accidental deficiency of clerks above the serum cholesterol median in area II-C The data are presented in Table Cl 26

Table Cl 27 presents the distribution of smoking habits in the switchmen and clerks in the several areas The only *important difference* occurred *in the* switchmen in area III who were characterized by fewer heavy smokers (more than 20 cigarettes a day) and more non-smokers (quit and never smoked) than in the other areas

Differences in the Measured Variables between Occupations within Areas

Inspection of the data revealed that important differences existed between sedentary clerks and switchmen in relative body weights and in skinfolds The medians of these two variables are plotted by age and occupation for the major geographic areas in figures Cl 11 and Cl 12 while figures Cl 13 and Cl 14 present the data by age and occupation (areas combined) for each of the four variables The significance of the differences is assessed by data present*ed in Table Cl 28 These data* were developed from area and age specific distributions of the combined occupations (switchmen plus sedentary clerks) The observed and expected *numbers* of men above both the median and the 80th percentile (of the distribution of the combined occupations) were determined for each age group

Switchmen had heavier relative body weights than clerks in area I and in the total for all areas The excess in numbers of switchmen above the medians *and 80th percentiles* of combined occupations are statistically significant for area I (chi-square for median cut *20 64* for 80th percentile *7 79*) and for the total of all areas (chi-square for median cut 14 91 for 80th percentile *5 20*) While in area II the excess number of switchmen above the median *yields a chi-square of 5 74 the distinction fails to appear at the 80th percentile*

On the other hand switchmen appear to be leaner than clerks on the basis of Σ *skinfold* medians in the total for all areas (chi-square *4 94*) but this distinction is largely accounted for by *the occupational difference in the* Rocky Mountain area (III) where only 39 6 % of the switchmen were found to have Σ *skinfold measurements above the* combined median (chi-square 9 51) and only 15 1 % above the 80th percentile

TABLE Cl 28

Men expected (E) and observed (o) above age and area specific medians of the combined distribution of clerks and switchmen in the geographic areas for each of five measured variables

Area	Sedentary Clerks E	O	O/E	Switchmen E	O	O/E
Relative Body Weights						
I	128 5	102	0 79	123 5	149	1 20
II	175 0	157	0 89	150 5	164	1 09
III	26 5	30	1 13	52 0	47	0 90
IV	88 5	86	0 97	80 0	82	1 02
All	418 5	375	0 90	406 0	442	1 09
Σ Skinfolds						
I	130 0	133	1 02	125 5	121	0 96
II	180 5	187	1 04	155 0	144	0 93
III	27 0	36	1 33	53 0	42	0 79
IV	89 5	90	1 01	82 0	81	0 99
All	427 0	446	1 04	415 5	388	0 93
Systolic Blood Pressure						
I	129 5	129	1 00	125 5	124	0 99
II	181 0	192	1 06	155 0	140	0 90
III	27 0	30	1 11	53 0	48	0 91
IV	89 5	95	1 06	82 0	75	0 92
All	427 0	446	1 04	415 5	387	0 93
Diastolic Blood Pressure						
I	129 0	116	0 90	125 5	137	1 09
II	180 5	187	1 04	155 0	149	0 96
III	27 0	29	1 07	52 5	48	0 91
IV	89 5	104	1 16	82 0	70	0 85
All	426 0	436	1 02	415 0	404	0.97
Serum Cholesterol						
I	129 5	122	0 94	122 5	130	1 06
II	177 5	171	0 96	152 0	153	1 01
III	26 5	29	1 09	53 0	49	0 92
IV	88 5	84	0 95	79 5	83	1 04
All	422 0	406	0 96	407 0	415	1 02

TABLE CI 27

U S railroad area comparison of smoking habits Observed (O) and expected (E) numbers of non-smokers, moderate and heavy smokers and chi-squares Expected numbers based on men in all areas for each occupation and age class Non-smoker= never and quit, moderate=10-20 cigarettes per day; heavy=more than 20

		Switchmen				Clerks			
	Area	O	E	Ratio	Chi^2	O	E	Ratio	Chi^2
Non-smokers	I	80	91 5	0 87	n. s	129	125 4	1 03	n. s
	II	112	108 2	1 04	n. s	170	174 9	0 97	n. s
	III	47	37 4	1 26	3 88	25	25 7	0 97	n. s
	IV	57	59 0	0 97	n. s	87	85 3	1 02	n. s
Moderate smokers	I	70	73 0	0 96	n. s	81	75 5	1 07	n. s
	II	82	89 2	0 92	n. s	98	105 5	0 93	n. s
	III	32	30 8	1 04	n. s	14	16 1	0 87	n. s
	IV	57	48 0	1 19	n. s	57	52 9	1 08	n. s
Heavy smokers	I	84	75 3	1. 12	n. s	37	43 4	0 85	n. s
	II	99	95 2	1 04	n. s	71	61 0	1 16	n. s
	III	22	33 5	0 66	6 03	13	9 0	1 44	n. s
	IV	48	48 9	0 98	n. s	22	30 1	0 73	n. s

TABLE Cl 28

Men expected (E) and observed (o) above age and area specific medians of the combined distribution of clerks and switchmen in the geographic areas for each of five measured variables

	Sedentary Clerks			Switchmen		
Area	E	O	O/E	E	O	O/E
Relative Body Weights						
I	128 5	102	0 79	123 5	149	1 20
II	175 0	157	0 89	150 5	164	1 09
III	26 5	30	1 13	52 0	47	0 90
IV	88 5	86	0 97	80 0	82	1 02
All	418 5	375	0 90	406 0	442	1 09
Σ Skinfolds						
I	130 0	133	1 02	125 5	121	0 96
II	180 5	187	1 04	155 0	144	0 93
III	27 0	36	1 33	53 0	42	0 79
IV	89 5	90	1 01	82 0	81	0 99
All	427 0	446	1 04	415 5	388	0 93
Systolic Blood Pressure						
I	129 5	129	1 00	125 5	124	0 99
II	181 0	192	1 06	155 0	140	0 90
III	27.0	30	1 11	53 0	48	0 91
IV	89 5	95	1 06	82 0	75	0 92
All	427 0	446	1 04	415 5	387	0 93
Diastolic Blood Pressure						
I	129 0	116	0 90	125 5	137	1 09
II	180 5	187	1 04	155 0	149	0 96
III	27 0	29	1 07	52 5	48	0 91
IV	89 5	104	1 16	82 0	70	0 85
All	426 0	436	1 02	415 0	404	0 97
Serum Cholesterol						
I	129 5	122	0 94	122 5	130	1 06
II	177 5	171	0 96	152 0	153	1 01
III	26 5	29	1 09	53 0	49	0 92
IV	88 5	84	0 95	79 5	83	1 04
All	422 0	406	0 96	407 0	415	1 02

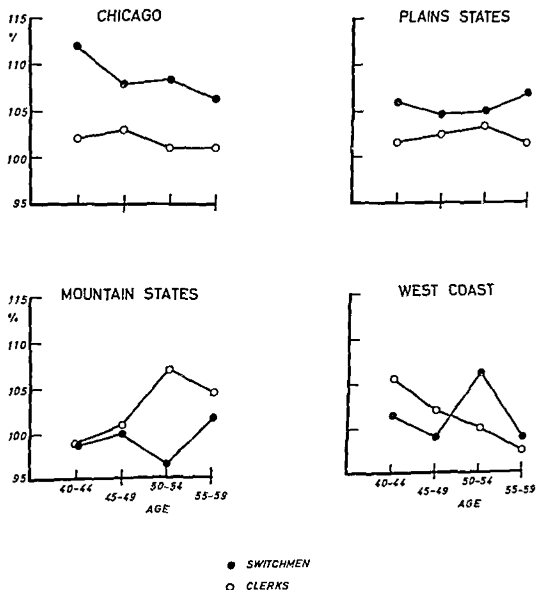

MEDIAN RELATIVE BODY WEIGHT BY GEOGRAPHIC AREA
U S RAILROAD SWITCHMEN and SEDENTARY CLERKS
CHICAGO
PLAINS STATES
MOUNTAIN STATES
WEST COAST
115
%
110
105
100
95
40-44
45-49
50-54
55-59
AGE
SWITCHMEN
CLERKS

Figure Cl 11

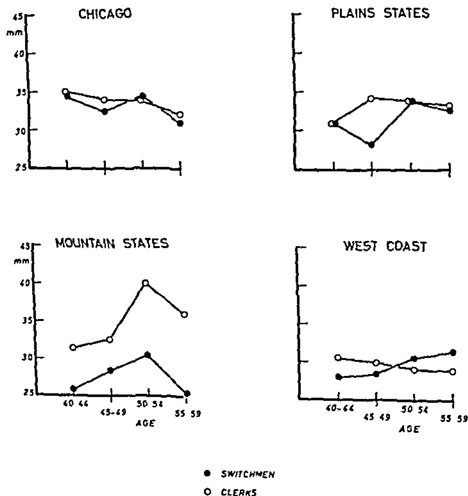

MEDIAN SUM OF SKINFOLDS BY GEOGRAPHIC AREA
U S RAILROAD SWITCHMEN and SEDENTARY CLERKS
CHICAGO
PLAINS STATES
MOUNTAIN STATES
WEST COAST
45
mm
40
35
30
25
40 44
45-49
50 54
55 59
AGE
40-44
45 49
50 54
55 59
AGE
● SWITCHMEN
O CLERKS

Figure Cl 12

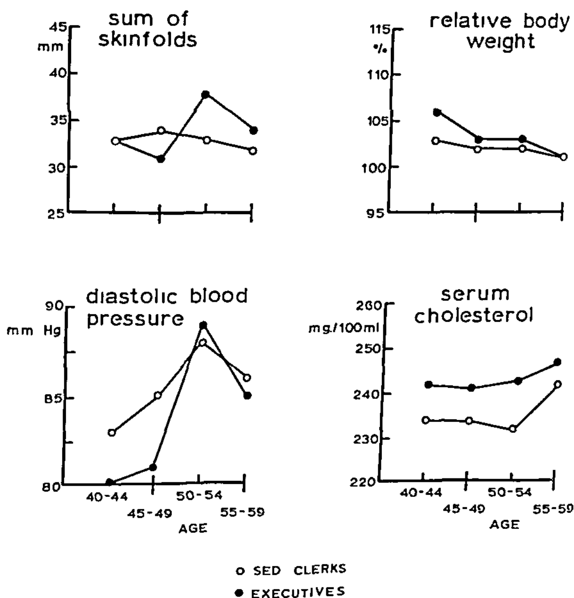

US RAILROAD MEN
medians - all geographic areas combined
sum of skinfolds
45
mm
40
35
30
25
relative body weight
115
%
110
105
100
95
diastolic blood pressure
90
mm Hg
85
80
40-44
45-49
50-54
55-59
AGE
serum cholesterol
260
mg/100ml
250
240
230
220
40-44
45-49
50-54
55-59
AGE
o SED CLERKS
• EXECUTIVES

Figure CI 13

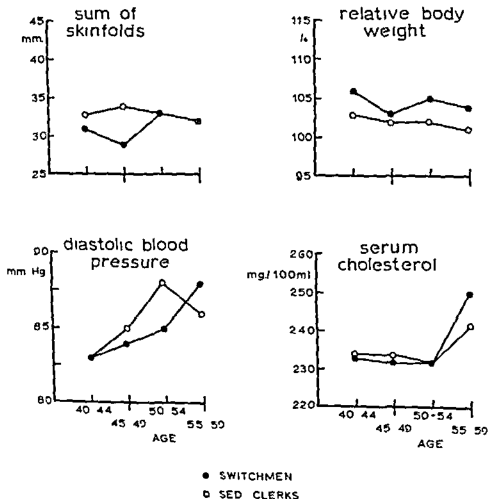

U S RAILROAD MEN
medians - all geographic areas combined
sum of skinfolds
mm.
45
40
35
30
25
relative body weight
%
115
110
105
100
95
diastolic blood pressure
mm Hg
90
85
80
40 44
45 49
50 54
55 59
AGE
serum cholesterol
mg/100ml
260
250
240
230
220
40 44
45 49
50-54
55 59
AGE
SWITCHMEN
SED CLERKS

Figure C1 14

(chi-square 3 86) It is of interest to note that contrary to the general pattern of relative body weight relationships noted in the preceding paragraph, switchmen also had lower relative body weights than clerks in area III, but the difference is not statistically significant This, however, is consistent with the earlier observation that Rocky Mountain switchmen were noticeably lighter for their height and age than switchmen in other areas

It is of considerable interest that removal of area III switchmen and clerks from the all area totals reduces the occupational difference to a non-significant level both at the median and 80th percentile cutting points

In all areas fewer than 50 % of the switchmen had systolic blood pressures above the combined median In area II this deficiency is statistically significant (chi-square 3 93 at median, 4 14 at 80th percentile) For all areas combined only 41 6 % of switchmen exceed the median systolic blood pressure resulting in a chi-square value of 5 51 The distributions of diastolic blood pressures follow essentially the same pattern except for area I where switchmen seem to have somewhat higher pressures than clerks on the basis of the median cut (chi-square 4 35) There is however no statistical significance in the differential occurrence of diastolic hypertension (defined as values exceeding the 80th percentile) in any area

Occupational differences in the distribution of serum cholesterol concentrations were not demonstrable though in most areas the values found among switchmen tended to be higher than those found in clerks The one area exception was found in the Rocky Mountains (area III) where the reverse was true but none of the differences approached statistical significance

The observed and expected numbers about the area and age-specific medians were next combined by age and occupation (for all areas) in order to determine whether any of the occupational differences are related to age in a systematic fashion In all age groups less than 50 % of the clerks were found to have values of relative body weight above the combined median and less than 20 % above the 80th percentile but these deficiencies were of statistical significance only for the youngest (age group 40—44, chi-square 5 46) and oldest (age group 55—59, chi-square 4 08) subjects With the exception of the age group 50—54 a disproportionately large number of clerks fell above the Σ skinfold median and 80th percentile values but statistical significance is found only in age group 45—49 (chi square 6 87 for a median partition) Similarly though clerks consistently had systolic blood pressures above the median and 80th percentile values more frequently than switchmen in all age groups the tendency was statistically significant only among 50—54 year old men at the median (chi-square 4 60) With respect to diastolic blood pressures and serum cholesterol concentrations no occupational distinctions were demonstrable

Executives vs Sedentary Clerks

Executives have been compared to clerks as a group without consideration of area breakdown for reasons given above The medians of the measured variables by age of the two occupations are presented in Figure CI 13 The values of the medians suggested that the younger executives might have lower diastolic blood pressures than clerks and that executives might have higher serum cholesterol concentrations at all age groups However tests of significance of the differences in these variables in the two occupations demonstrated that only the systolic blood pressure difference was important Table CI 29 pre-

TABLE CI 29

Numbers of U S railroad executives observed (O) and expected (E) above the age specific medians and 80th percentiles for sedentary clerks for each of five measured variables and chi-squares Number of expected based on combined occupations

Medians

	O	E	Ratio	Chi-square
Σ skinfold	138	129 2	1 07	N S
Relative body weight	128	128 2	1 00	N. S
Systolic blood pressure	86	116 7	0 74	18 98
Diastolic blood pressure	131	127 5	1 03	N. S
Serum cholesterol	136	128 1	1 06	N S

80th Percentile

	O	E	Ratio	Chi-square
Σ skinfold	50	50 2	1 00	N S
Relative body weight	39	47 6	0 82	N S
Systolic blood pressure	32	46 2	0 69	6 44
Diastolic blood pressure	46	49 5	0 93	N S
Serum cholesterol	41	48 0	0 85	N. S

sents the observed and expected numbers of executives found above the values of the age specific medians and 80th percentiles of the sedentary clerks along with chi-squares When the data were examined by age groups it was found that significantly fewer executives than expected had systolic blood pressures above the value at the median in the 40—44 year old group (chi-square 12 62) and the 55—59 year old group (chi-square 6 68) at the 80th percentile the same age groups showed fewer men than expected above the cutting point but the 40—44 age group just failed to reach the conventional value of chi-square which is considered significant (chi-square 3 61) and the oldest 5-year group was non-significant (chi-square 2 41)

Non-Sedentary Clerks vs Sedentary Clerks

The cumulative distributions of the measured variables show little or no difference between non-sedentary clerks and sedentary clerks in height relative body weight Σ skinfolds and serum cholesterol concentration But in blood pressures there are differences which appear to be large and are reversed with age Non-sedentary clerks in the ages 40—49 have lower systolic and diastolic blood pressures than sedentary clerks while at ages 50—59 the reverse appears to be true

The significance of the differences was evaluated by comparing the number of non-sedentary clerks whose systolic and diastolic blood pressures were above the median and 80th percentile of the sedentary clerk group for each of the five-year age groups None of the chi-square values based on the median cutting points reached significance in the four systolic and four diastolic blood pressure comparisons However difference between the occupations in systolic blood pressure at ages 40—44 gave chi-square 3 71 and in diastolic blood pressure for the 45—49 year old group the value was chi-square 3 54 The analysis based on the 80th percentile reference point yielded only one chi-square value of significance (4 29), that for the systolic blood pressure in the 55—59 year old group

The small numbers of non-sedentary clerks in the separate age groups (N = 32 at 40—44 N = 39 at 45—49 N = 38 at 50—54 N = 47 at 55—59 years) make it difficult to draw firm conclusions regarding this group especially in view of accidents of classification and job selection

Comparison of Early Employment and Survey Examination Data

It has been recognized for many years that hiring practices of management and personal preferences of employees may result in special situations in an excess of disease-prone individuals in a particular occupation Morris *et al* (1956) provided evidence derived from uniform size measurements that men hired as conductors (a physically active job) were not as fat at the time of employment as those hired to drive the busses (a relatively inactive job) When these men were examined at the age of 40 to 59 the drivers were found to be more overweight than the conductors In this case the characteristic of "overweightness" among drivers as compared to conductors was at least in part the result of selection at the time of first employment

Evidence for this kind of selection among the railroad employees was sought by examining the records of employment examinations or the first examination of record during the early years of employment Due to long standing policy of management it was not possible to examine these records

on certain railroads However systolic and diastolic blood pressures and age at the time of examination were obtained on 417 switchmen and 297 clerks who were 40—59 in 1958—59 The age range at the time of the first examination was 17 to 49 on both switchmen and clerks and the medians were in the age range of 30 to 34 years

Height weight and age data at the first examination were found in 381 clerks and 405 switchmen who had been examined in 1958—59 In this group the median for the relative body weights at the first examination for the clerks was in the 20—24 year old age class and in the 30—34 age group for the switchmen

The data are not ideal since the groups are not random samples and are deficient in data on clerks because certain railroads did not keep such records Age-adjusted quartiles and age adjusted cumulative frequencies were constructed to look for differences between clerks and switchmen The age-adjusted cumulative frequencies for the several variables are presented in Figures C1 15 through C1 18 Initially clerks were slightly taller than switchmen but at the time of the survey examination the switchmen were taller than the clerks perhaps the physical activity required of the switchmen helped them maintain a more upright posture Switchmen had a larger body weight at the first examination and this relationship was maintained at the survey examination In both systolic and diastolic blood pressure the initial data showed almost identical cumulative frequencies On the other hand at the survey examination the clerks tended to have higher blood pressures than the switchmen but the difference did not reach statistical significance There is evidence then that occupational selection was in large part responsible for the difference in relative body weight observed at the time of the survey On the other hand there was no evidence that the blood pressure was influenced by the occupation indeed it appears if anything that the occupation tended to result in a higher systolic and diastolic blood pressure in clerks

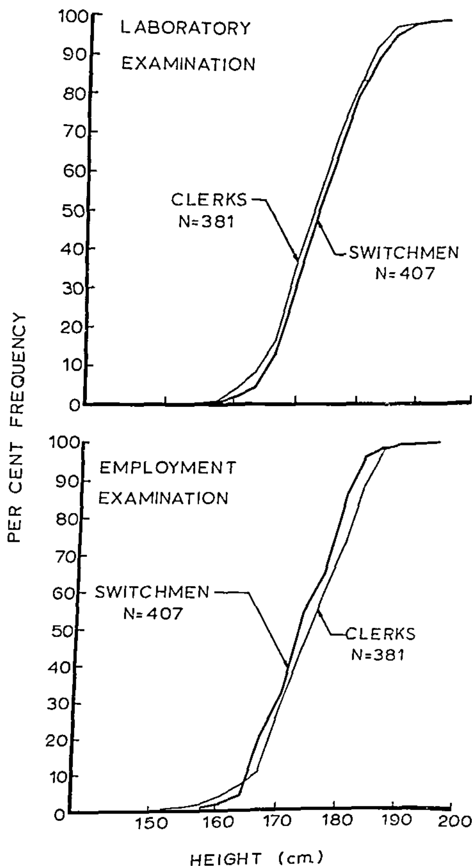
Another example of occupational selection of a characteristic appears in the data on height The executives are consistently taller than either clerks or switchmen Since changes in height with age are small it appears reasonable to conclude that the executives were taller than either clerks or switchmen when they were first employed in the railroad industry

The Estimation of Prevalence of Coronary Heart Disease among Men Differing in Physical Activity

Technical difficulties in estimating physical activity of individuals have caused investigators to rely mainly on classification by occupations The present discussion will focus on problems in estimating the relative prevalence of coronary heart disease among men employed in physically active and sedentary occupations

The roster of men aged 40 to 50 in any occupation is constantly changing as men are leaving and entering the occupation for many reasons With the aid of U S Railroad Retirement Board records some estimates of this turnover can be made Study of a 4 per cent sample of all men employed by the railroads in the United States in 1954 revealed that 68 per cent of the clerks 77 per cent of the switchmen and 56 per cent of the maintenance-of-way employees were still in the same occupation at the end of 6 years

During the 6 year period 3.3 per cent of the clerks age 40 to 59 at the start left the railroad industry 17 per cent changed jobs within the industry



LABORATORY
EXAMINATION
CLERKS
N=381
SWITCHMEN
N=407
EMPLOYMENT
EXAMINATION
SWITCHMEN
N=407
CLERKS
N=381
PER CENT FREQUENCY
HEIGHT (cm.)
0
10
20
30
40
50
60
70
80
90
100
150
160
170
180
190
200

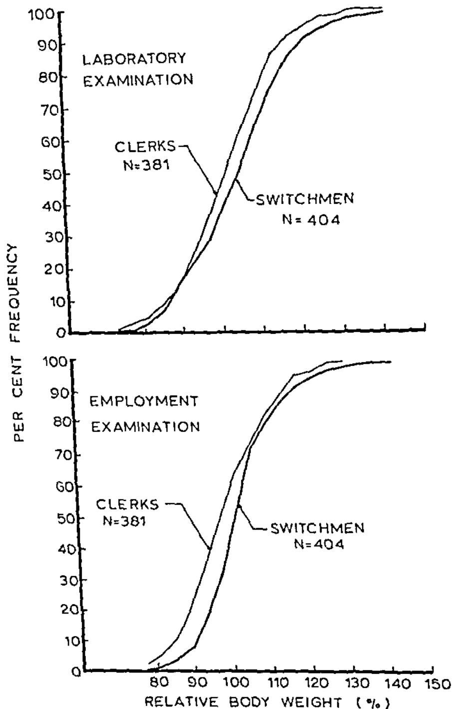
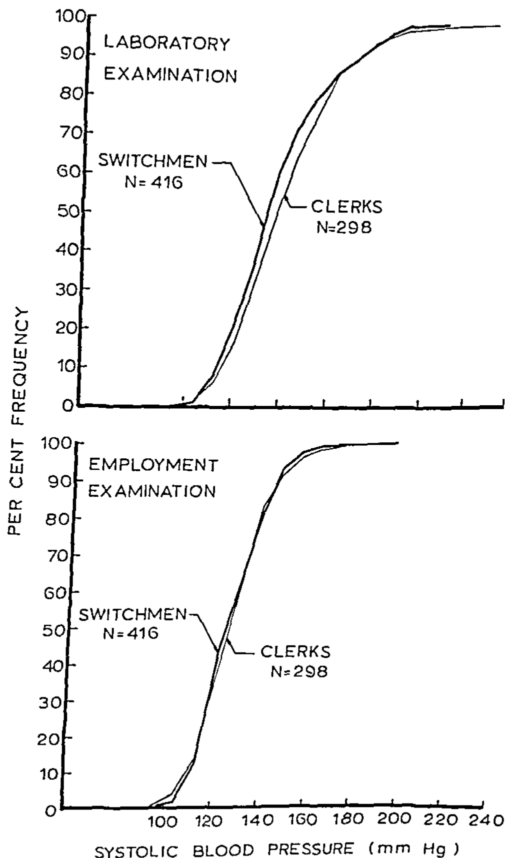
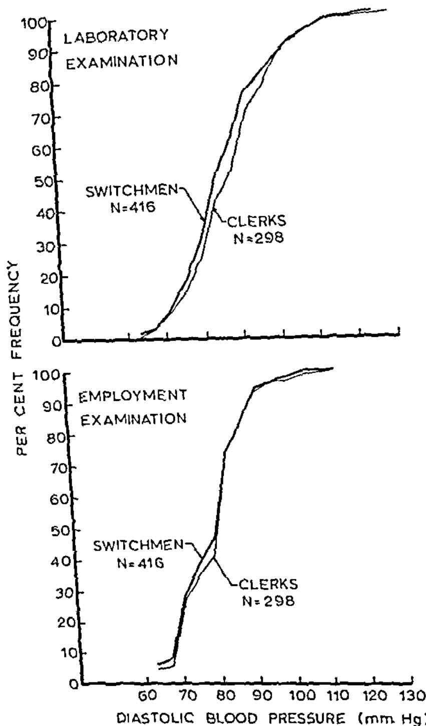
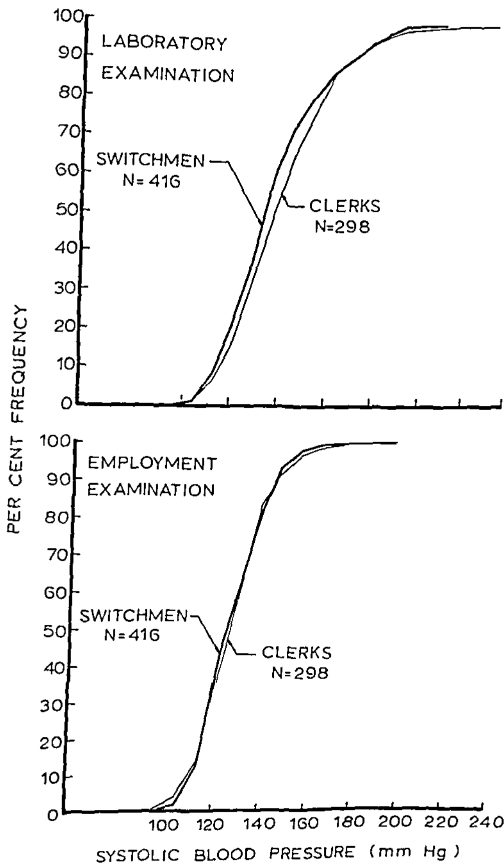

LABORATORY
EXAMINATION
CLERKS
N=381
SWITCHMEN
N=404
PER CENT FREQUENCY
100
90
80
70
60
50
40
30
20
10
0
EMPLOYMENT
EXAMINATION
CLERKS
N=381
SWITCHMEN
N=404
80 90 100 110 120 130 140 150
RELATIVE BODY WEIGHT (%)

Figure C1 16


LABORATORY EXAMINATION
SWITCHMEN N=416
CLERKS N=298
EMPLOYMENT EXAMINATION
SWITCHMEN N=416
CLERKS N=298
PER CENT FREQUENCY
0
10
20
30
40
50
60
70
80
90
100
100
120
140
160
180
200
220
240
SYSTOLIC BLOOD PRESSURE (mm Hg)


LABORATORY
EXAMINATION
SWITCHMEN
N=416
CLERKS
N=298
PER CENT FREQUENCY
EMPLOYMENT
EXAMINATION
SWITCHMEN
N=416
CLERKS
N=298
0
10
20
30
40
50
60
70
80
90
100
60
70
80
90
100
110
120
130
DIASTOLIC BLOOD PRESSURE (mm. Hg)


LABORATORY EXAMINATION
SWITCHMEN N=416
CLERKS N=298
EMPLOYMENT EXAMINATION
SWITCHMEN N=416
CLERKS N=298
PER CENT FREQUENCY
0
10
20
30
40
50
60
70
80
90
100
100
120
140
160
180
200
220
240
SYSTOLIC BLOOD PRESSURE (mm Hg)

of clerks and switchmen who actually developed coronary heart disease before moving out of the occupation data in a 5 year follow-up were obtained by searching the files of the Railroad Retirement Board for disability retirements of the men who had been examined as participants in the survey described here

Among the examined personnel 10 sedentary clerks and 6 switchmen were found who sought and obtained disability retirement awards because of documented coronary heart disease These withdrawals from active service indicate the magnitude of the selective influence which precedes the initial survey examination These numbers though small increase in importance when compared with the 41 cases of clinical coronary heart disease (including angina pectoris) found among sedentary clerks and 18 cases found among switchmen in the initial examination of the invited sample

That this influence may operate differentially among clerks and switchmen or among examinees and no-shows can be suggested by consideration of the following distribution of disability retirements for coronary heart disease (rates per 100 in parenthesis)

Age	Examined Sample		Invited Sample	
	Sedentary clerks	Switchmen	Sedentary clerks	Switchmen
40—49	0 (0 0)	5 (0 9)	0 (0 0)	6 (0 7)
50—59	10 (2 1)	1 (0 3)	12 (1 9)	11 (1 9)
Total	10 (1 1)	6 (0 6)	12 (1 0)	17 (1.3)

Among men who submitted to examination retirements tended to occur more frequently among clerks than among switchmen Among the "no-shows" the occupational difference is of the same order of magnitude but in the opposite direction It is interesting to also note that these retirements tended to occur in the younger decade among examined switchmen and in the older decade among clerks The numbers of cases here are very small and it is clear that more extensive studies of withdrawal due to coronary heart disease are needed It happens however that these preliminary data are consistent with the suggestion found in the death data i e that the occupational mobility of switchmen with coronary heart disease is greater than that of clerks

Mobility and occupational conditions present other problems in prevalence rates It is difficult to obtain information on all men in the desired age group unless both management and labor agree to making the survey examination mandatory In the current study on men in U S Railroads only 74 per cent of the clerks and 59 per cent of the switchmen were examined It is of interest to examine coronary heart disease withdrawal rates in the examined and "no-show group to investigate the distribution of coronary heart disease between these examined and those who refused For this purpose deaths ascribed to coronary heart disease which occurred in retirement or in other occupations as well as in-service in-original occupation were pooled with disability retirements because of coronary heart disease Since the actual examinations were carried out in 1957—59 (70 men were examined in the spring of 1960) the follow-up time is variable However clerks and switchmen were examined in equal numbers each year so that neither occupational group has an elapsed time advantage. The population at risk was calculated on the basis of age in 1958

4 8 per cent sought and obtained disability retirements and 5 7 per cent died The lower mobility of the switchmen was *due principally to the fact that* only 9 4 per cent moved to new jobs within the industry Disability retirement among switchmen was of the same order of magnitude The maintenance-of-way employees showed a different pattern with 6 9 per cent leaving the industry and 24 3 per cent taking other *jobs within the industry* Disability retirements accounted for approximately 9 per cent of the original cohort of maintenance-of-way employees

With respect to changing activity within an industry Kahn (*1963*) studied white postal clerks and carriers in Washington, D C who entered employment between *1906* and *1940* and found that 35 6 per cent of the carriers switched to clerical jobs while only 8 per cent of the clerks switched to the carrier category While in the *railroad industry, if one classifies the* physical activity of the jobs that the railroad employees moved into it *appears that roughly one-half of the* clerks took a new job at the same physical activity level while 92 per cent of the switchmen choosing a new occupation within the railroad industry did not change the level of the physical activity required by the job Two-thirds of the maintenance-of-way employees *changing jobs moved to an* occupation in which less physical activity was required It is clear that the mobility patterns are not the same in different occupations and each situation must be investigated separately In addition it can be inferred that the opportunity exists for differential effects on the distribution of one or more of the risk factors However there are no data to document this

A more important question is how the mobility of men who develop coronary heart disease compares with the over-all mobility rate of the occupation The first *indication from our data* is that the withdrawal rate of men either with the disease or who are destined to develop it is different from over-all occupational mobility Evidence supporting *this can be found by tabulating* the deaths from all causes that occurred in the 4 per cent sample of the cohort over the *follow-up period of 6 years* There were no differences in over-all mortality between switchmen and clerks who changed jobs On the other hand the deaths in retirement accounted for approximately 28 per cent of all deaths among switchmen and 18 per cent of all deaths among clerks These data *suggest that men with coronary heart* disease or with potential coronary heart disease were *leaving the switchmen's* group at *a faster rate than the clerks'*

Death rates over a 2-year period of all men employed in the railroad industry in the occupations of interest during 1954 were available for 1955 *and 1956 (Taylor et al 1962)* These were compared with a 6-year study of deaths in the same cohort which *includes deaths occurring in men* who have moved to other occupations or who had retired (Taylor *et al* unpublished data) There were *39 750* clerks and 30 237 switchmen age 40—59 in the cohort at the outset The numbers were large enough to allow one to calculate valid age-adjusted mortality ratios of deaths ascribed to coronary heart disease among switchmen and clerks *The mortality ratio (switchmen/clerks) of in-service in-occupation* coronary heart disease death rates was 0 69 *while that in the 6-year study was* 0 81 *These data suggest that the mobility* of switchmen with coronary heart disease was *greater than that of clerks but it* was *also clear that* many men who develop coronary heart disease *de novo after* leaving the ranks of the occupation were included *in the 6-year* follow-up study of deaths

To obtain evidence on the mobility

TABLE C1 30

Five year withdrawal rates ascribed to arteriosclerotic heart disease (deaths plus medical retirements) in the examined and "no-show" groups in a sample of sedentary clerks (N = 1088) and switchmen (N = 1424)

	Clerks				Switchmen			
	%	Withdrawals/100			%	Withdrawals/100		
Age	sample exam	exam	no-show	total	sample exam	exam	no-show	total
40-44	75 9	----	4 08	0 88	63 4	1 70	1 16	1 50
45-49	72 8	1 66	----	1 25	62 4	3 38	4 20	3 69
50-54	75 7	5 00	1 54	4 26	55.6	1 81	4 76	3 08
55-59	71 8	7 76	5 95	7 28	52 8	4 70	9 42	6 97
Age adjust rate	73 9	3 61	2 90	3 42	59 1	2 90	4 89	3 81

and the death and disability retirement data are complete up to 1 July 1964 The results are presented in Table C1.30 For both occupations the withdrawal rates for the "no-shows" are larger than those for the men examined but the difference between the two categories is not the same It is clear that a larger number of switchmen than clerks with actual or potential coronary heart disease refused examination It is equally clear that the prevalence rates are worse than useless in this situation since not only were coronary cases moving out of the population before the examination but differential occupational bias existed in recruitment

Experience with the railroad employees indicates that a man who develops angina pectoris is confronted with a great variety of problems in trying to decide whether he should withdraw from the occupation of his choice particularly if his occupation required physical activity He is usually at an age when it is difficult to obtain another form of employment outside the railroad industry seniority regulations also make seeking a job in another railroad craft difficult and disability retirement benefits do not provide financial support at a desirable level The result frequently is that he seeks consultation with a private physician and then waits for some time before he makes up his mind about what he is going to do Alternatively he may avoid physicians at all costs during a long period of indecision Employment is occasionally changed (if the opportunity arises) without consulting a physician Behavior in other industries and occupations may differ but this matter needs consideration if angina pectoris is to be counted as evidence of coronary heart disease

These facts must be considered in evaluating prevalence in any study in which physical activity is inferred from occupational classification Studies such as those of Brown et al, (1957), of a heterogeneous population simply make the situation more complicated since it is necessary to have some knowledge of factors affecting disability retirements and occupational changes in each of the many occupations

Studies in which incidence is estimated over a very short period of time (compared to the length of time that elapses before a man with angina dies has an infarction or consults a physician for the first time) and in which the population was not examined at the beginning of the incidence period are open to question because the reservoir of unreported angina is unlikely to be identical in active and sedentary occupations and some of these cases may move out of the population under study because of what appears to be voluntary retirement or change in occupation Questions of this type can be raised regarding the studies of Zukel et al (1959) in which an area was studied, and Morris et al (1953) in which occupations were studied It appears that the majority of the factors affecting observed prevalence rates operate to exaggerate any true excess that may exist in an active population over that in a sedentary population

Summary

Data on a population for study of 8 053 clerks switchmen and executives were assembled with the cooperation of 20 railroad companies operating in the northwest quadrant of the United States A sample of 1163 sedentary clerks, 1414 switchmen and 363 executives who were located in 26 separate towns and cities was selected for examination which was conducted in a mobile laboratory parked close to the place of work Of those invited 73 9 per cent of the sedentary clerks (N=859) 59 1

concentrations were not different between occupations within geographical areas or within occupations between geographical areas

Executives differed from sedentary clerks only in that the systolic blood pressure of the executives was lower than that of the clerks

The most striking difference between switchmen and clerks was the difference in relative body weight and to a lesser degree the difference in systolic blood pressure Examination of employment records revealed that there was no difference in the blood pressure of clerks and switchmen at the time of employment but that the switchmen had larger relative body weights than the clerks at the time they entered the industry The difference persisted until the survey examination which occurred from 10 to 38 years later It was concluded that occupational selection played an important role in the results A second example of occupational selection was seen in the height difference between executives and both switchmen and clerks

Data are presented to illustrate the problems of estimating the true prevalence of coronary heart disease in the physically active as compared to the sedentary occupations In this study the observed prevalence of coronary heart disease was influenced by greater withdrawal of younger switchmen with coronary heart disease as compared to clerks and selection against the experiment by switchmen with coronary heart disease

Acknowledgments

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Mr Ernest Klepetar the Nationwide Insurance Companies provided advice on design and selected the clump samples for examination Dr Jaakko Kihlberg gave assistance in the early stages of statistical analysis The final statistical analysis was designed by Dr Ancel Keys

Valuable help was also provided by Mrs Nedra Foster Mr Walter Carlson Mrs Joan Blomqvist Mrs Gail Dolliff Mrs Gayle Olson Miss Patricia Northrup and Mrs Marie Nyquist. The following individuals gave much assistance during their predoctoral training periods Dr Christa Eckert, Dr Warren Kinsey Dr Larry Rowell Dr John Gilbertson and Dr Ladislav Novak

Mr Clyde Pearson the Great Northern and Mr Downing Jenks the Rock Island provided important advice and encouragement Mr George M Harrison President the Brotherhood of Railway and Steamship Clerks Mr W P Kennedy President the Brotherhood of Railroad Trainmen and Mr Neil P Speirs President, the Switchmen's Union of North America endorsed and supported the project. Mr P Y Byers General Chairman the Brotherhood of Railroad Trainmen for the Northern Pacific and Mr F A Emme General Chairman the Brotherhood of Railway and Steamship Clerks for the Great Northern gave advice on union problems and attitudes at the local level

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Numerous members of cooperating brotherhoods and railroad companies gave much time advice and enthusiastic support

per cent of the switchmen (N=835) and 68.3 per cent of the executives (N=251) responded to the invitation and were examined In addition 156 men, classified as clerks by management but whose job required physical activity at a level above that considered sedentary were examined and are reported here as non-sedentary clerks It is estimated that the switchmen performed physical work which resulted in an energy expenditure per day of 600 kilocalories greater than that of the sedentary clerks In general the sedentary clerks had been in the railroad industry longer than switchmen but they changed jobs more often than switchmen The switchmen and clerks had a homogeneous distribution of parental nationality But the executives showed some differences in this respect Executives were more often married than switchmen who were more frequently married than clerks Both clerks and switchmen were on the same economic level

These American railroad employees were taller, fatter, and heavier for their height and age and had higher serum cholesterol concentrations than the average of all the groups as a whole Switchmen were heavier cigarette smokers than either sedentary clerks or executives The analysis of the classification of the electrogardiograms showed no important difference in Q items between occupations nor were there any differences of consequence in other resting items However the prevalence of post-exercise S-T depressions was significantly larger in clerks than in switchmen The prevalence of hypertension was not remarkably different in the three occupations The executives had fewer numbers of men with diastolic blood pressures above the criteria But all the groups had a higher prevalence of hypertension than the mean of all the other groups in the study The prevalence of hypertension increased with increasing relative body weight in all groups but only switchmen and clerks had an increase of hypertension with increasing fatness as measured by the sum of the skin folds When the three occupations were pooled prevalence of hypertension increased with increasing serum cholesterol concentration The prevalence of overweight was greatest among switchmen and least among clerks The frequency of overweight men increased with increasing systolic and/or diastolic blood pressure in switchmen and clerks but this was only true of diastolic blood pressure in executives

The sedentary clerks and switchmen were tabulated by geographic areas in which the West Coast had the highest reported death rate from coronary heart disease and the Rocky Mountain area the lowest The "plain states" area (defined as that portion east of the Rocky Mountains and west of Chicago-Milwaukee) and Chicago-Milwaukee had intermediate coronary heart disease death rates The distributions of the measured variables in clerks were uniform in these areas Switchmen had large differences in distributions of relative body weight skinfold and blood pressures In the Milwaukee-Chicago area switchmen were found to be both heavier and fatter than in the other areas The Rocky Mountain switchmen were thinner and lighter had lower blood pressures smoked less and had a shorter period of employment in the railroad industry than the other switchmen There was no difference in the measured variables between the men living in small towns and large cities

Switchmen were heavier and thinner than the clerks when taken as a group But the difference in skinfolds between occupations does not reach significance if the switchmen and clerks in the Rocky Mountains are removed from the analysis The serum cholesterol

concentrations were not different between occupations within geographical areas or within occupations between geographical areas

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C2 MEN IN RURAL ITALY

by Flaminio Fidanza (Naples), Vittoria Puddu (Rome) Alfonso del Vecchio (Milan) and Ancel Keys (Minneapolis)

Introduction

Considerations of diet were prominent in the selection of geographical areas in Italy for comparative studies on cardiovascular disease in stable rural populations Nicotera a village in the far south of Italy was originally selected as an area for study because the diet was believed to be high in olive oil but low in other fats and because from local contacts in the area it seemed likely that such good cooperation would be obtained from the population that substantially all middle-aged men could be covered in detailed examinations These expectations were borne out in the subsequent experience

For comparison it was desired to study another rural area in Italy in which the habitual diet would be far richer in fat especially of the saturated type The lower part of the Po River valley is commonly believed by Italians to have such a diet In that area the village of Crevalcore seemed suitable because of population size distance from urban centers and offered cooperation Finally excellent local contacts and facilities were available in the village of Montegiorgio and it was considered likely that the diet there might be intermediate between that of Nicotera and Crevalcore in regard to fats

In all three areas the aim of examining a very high percentage of all men in the specified age range was achieved For Nicotera this coverage was 97 0 per cent the corresponding figures for Crevalcore and Montegiorgio were 98.5 and 99 0 per cent respectively In almost all cases it was possible to obtain some useful information from and about the men who refused or were unable to participate in the detailed examinations It is believed to be unlikely that any cases of clinical cardiovascular disease were in the non-examined group

The Area of Nicotera

Before the rise of Rome Greek colonizers settled on the lowland close to the shore of the Tyrrhenian Sea about 60 kilometers north of the Straits of Messina (the water between Scylla and Charybdis of classic history) Later they established Nicotera in a more defensible position several hundred meters higher on a spur of the mountains overlooking the sea and the small hamlet of Nicotera Marina close below

The main railroad line from Naples and the north of Italy passes through Nicotera Marina on the way to Reggio Calabria and Sicily but only a few local trains pause there Nicotera itself is not far off the main highway from the north to the toe of Italy but the secondary branch road from the highway to Nicotera carries only a little local traffic no one goes through Nicotera en route to someplace else

Nicotera produces olives grapes figs wheat some flowers for the perfume trade and for local use a little meat and poultry The climate is warm-temperate with a long hot dry season A few families at Nicotera Marina are engaged in fishing There is no manufacturing industry The population is poor and there is a steady migration of young people away from the area to other parts of Italy and overseas but beyond the age of 30 or so the population is relatively stable An indication of the poverty of the area is the fact that six of the men in the sample examined in September-October 1957 then aged 45—64 claimed no occupation save begging All in all Nicotera seems to be reasonably typical of the rural far south of Italy a backwards area of the depressed Mezzogiorno As elsewhere in many parts of Italy the people live in a crowded village and walk out daily to work in their small fields as far as several kilometers away

There were eight physicians in or near Nicotera in 1957 but the nearest modern diagnostic and treatment facilities are in a small hospital some 20 kilometers inland at Vibo Valentia The headquarters for the survey examinations was a rented two-storey house in the center of Nicotera

The Area of Crevalcore

The large agricultural village of Crevalcore is in the *fertile valley* of the Po River roughly equidistant from Modena and Bologna but north of the main highway between those cities This is in the relatively prosperous area called Emilia la grassa (Emilia the fat land) because of its abundant farm produce and traditionally rich diet Politically Crevalcore is Communist-controlled the consensus of opinion seemed to be that the local government is honest efficient and tolerant Wheat and other grains fruit and livestock dominate agriculture and there is no manufacturing industry The climate is hot in summer and relatively damp and cold in winter

Crevalcore like the other villages in this flat countryside could never have been militarily defensible so there was no fortress development and it is relatively spread out over the countryside The population beyond the age of 30 or so is fairly stable but besides the usual emigration of youth there is some movement at older ages to jobs in industry in nearby Bologna and elsewhere in Italy

There is a small but relatively complete hospital in Crevalcore and this was used as the headquarters for the survey examinations

The Area of Montegiorgio

Montegiorgio is a farming village in the rolling hills of the Province of Marche 35 kilometers inland by way of a secondary road from the small town of Fermo on the Adriatic coast The village itself is on the top of a hill but the families of the commune are spread out over several kilometers This was the land to which the Sabines fled from the famous rape but the population was early amalgamated with the advancing Roman Empire and Ancona now as then the largest city of the region was the springboard for the

invasion by Diocletian of Illyria (Yugoslavia)

Agriculture is the only industry in Montegiorgio, the small farms produce a good yield of produce but at a high cost of labor The climate is temperate but relatively cold in winter and there is generally abundant water from the nearby mountains The people are largely self-sufficient for everyday *needs from their own farms, or the* farms they operate as share-croppers, but the cash income is low There is a steady migration from all of Marche to urban centers and it is said that a quarter of a million "Marchigiani" are in Rome However the men aged 40 or more are generally stable in their *residences in or near the village*

Montegiorgio has a small hospital with a friendly chief physician and staff but the headquarters for the survey examinations was in a commodious suite of rooms in the town hall recently rebuilt and enlarged after an earthquake

Sample Coverage

The general method of establishing the rosters has been described in the preceding Section A, 12 and details of the method were given there for *Nicotera as an example* Though theoretically everyone in Italy is officially registered and every adult must *have a valid identity card the local* registries are not always up to date or free from clerical error It is not uncommon for a man to move away from his legal residence but to have his name carried on the local voter registry for years thereafter *However the correction* of errors and establishment of a true roster is much easier in villages such as Nicotera Crevalcore and Montegiorgio where everyone knows everyone else than in urban areas where people are less stable and are easily lost in the moving crowd Since there is practically no immigration into these villages, the discovery of new comers is not troublesome

The aim was to examine all the men aged 40—59 (45—64 in Nicotera) in these villages The high degree of *success in this aim is indicated by the* fact that the examinations covered 97 0 98 5 and 99 0 per cent of the men in the corrected rosters of Nicotera Crevalcore and Montegiorgio respectively However by the time the men were actually examined a few of them were aged 60 and in some other *cases the ages stated in the rosters* were found to be incorrect when identity cards were compared Since the present analysis concerns only men aged 40—59 at the time of examination the numbers for whom data given here are smaller than the total number of men examined

Age Distribution

The age distributions of the men in these Italian villages show some peculiarities At Nicotera the men aged 45—49 50—54 and 55—59 represented 48 9 26 2 and 24 9 per cent of all men aged 45—59 The large relative excess of men aged 45—49 (in 1957) is striking At least part of the explanation is that their cohort born in the years 1908 through 1912 was too *young to* have suffered the heavy attrition from mortality in World War I or from migration in the difficult *postwar period through the mid-*twenties that affected the men born in the period 1893—1907 i e the men in *the age groups 50—54 and 55—59*

Both Crevalcore and Montegiorgio show a different set of peculiarities in age *distribution — a great shortage of* men aged 40—44 and a less marked shortage of men aged 55—59 At Cre*valcore the percentages of all men aged*

40—59 who were aged 40—44 45—49 50—54 and 55—59 were respectively 17.5 30 5 29 7 and 22.3 The corresponding percentages at Montegiorgio were 17 2 34 4 30.3 and 18 1 Men aged 40—44 in 1960 were born in 1916—1920 a period of a very low birth rate in Italy as in many other countries caused by World War I This cohort was also the first to be called to the army when World War II began and therefore was the one most affected by mortality and by reluctance to return to the restrictions of village life after the war

The deficiency of men aged 55—59 in Crevalcore and Montegiorgio that is to say of men born in the years 1900—1904 may have several explanations Their birth dates are included in the period when emigration from Italy of young men and young families was at its height Perhaps more important this was a cohort much affected by the great postwar migration to the cities and away from Italy in the nineteen-twenties

Age, Physical Activity and Occupation

Table C2 1 gives the distribution of the men of Nicotera Crevalcore and Montegiorgio by 5 year age groups into three classes of habitual physical activity In all areas the majority of these middle aged men were engaged in heavy physical work mostly as small-scale farmers Except in Crevalcore there was a tendency for the men to withdraw from the heaviest labor in their late fifties but even at ages 55—59 more than half of the men in all areas were in Activity Class 3

The occupations of all of the men were ascertained but for the present purposes it seemed desirable only to differentiate between the higher socio-economic group of professional and businessmen the men in agricultural occupations and all others These groupings are given in Table C2 2 The dominance of farming is clear as well as the fact that relatively few men in these villages could be put in the higher socio-economic class even when this was extended to include the salesmen (Code nos 14 and 15) Actually most of the few men who might be classed as salesmen in these areas were also semi independent businessmen By and large "upper socio-economic class in these villages is only a *relative term* No really rich men live in these villages and the teachers who are relatively upper class have lower incomes than many of the men in these areas who are rated in a lower social class

Distribution of the Measured Variables

Table C2 3 gives the median values by age for height relative body weight Σ skinfolds as a measure of body fatness systolic and diastolic blood pressure and cholesterol concentration in the blood serum Table C2 3 also gives these medians expressed as percentages of the averages of the medians for all 18 population samples in these cooperative studies

The men of Nicotera were the shortest thinnest men and had the lowest relative weights The men of Crevalcore were the tallest fattest and relatively heaviest The contrast is greatest in regard to body fatness The thickness of the true skin is about 1.5 mm so about 3 mm of the skinfold thickness is not fat and about 6 mm of the Σ skinfolds should be subtracted to get a measure of actual fat Accordingly the relative fat measure is about 7 mm for Nicotera 9 for Montegiorgio and 16 for Crevalcore. In other words the men of Crevalcore tend to be more than twice as fat as the men of Nicotera

There are similar differences between the areas in regard to blood

invasion by Diocletian of Illyria (Yugoslavia)

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Sample Coverage

The general method of establishing the rosters has been described in the preceding Section A 12 and details of the method were given there for Nicotera as an example Though theoretically everyone in Italy is officially registered and every adult must have a valid identity card the local registries are not always up to date or free from clerical error It is not uncommon for a man to move away from his legal residence but to have his name carried on the local voter registry for years thereafter However the correction of errors and establishment of a true roster is much easier in villages such as Nicotera Crevalcore and Montegiorgio where everyone knows everyone else than in urban areas where people are less stable and are easily lost in the moving crowd Since there is practically no immigration into these villages the discovery of newcomers is not troublesome

The aim was to examine all the men aged 40—59 (45—64 in Nicotera) in these villages The high degree of success in this aim is indicated by the fact that the examinations covered 97 0 98 5 and 99 0 per cent of the men in the corrected rosters of Nicotera Crevalcore and Montegiorgio respectively However by the time the men were actually examined a few of them were aged 60 and in some other cases the ages stated in the rosters were found to be incorrect when identity cards were compared Since the present analysis concerns only men aged 40—59 at the time of examination the numbers for whom data given here are smaller than the total number of men examined

Age Distribution

The age distributions of the men i these Italian villages show some pecu liarities At Nicotera the men age 45—49 50—54 and 55—59 represente 48 9 26 2 and 24 9 per cent of all me aged 45—59 The large relative exces of men aged 45—49 (in 1957) i striking At least part of the explana tion is that their cohort born in the years 1908 through 1912 was too young to have suffered the heavy attrition from mortality in World War I or from migration in the difficul postwar period through the mid-twenties that affected the men born in the period 1893—1907 i e the men in the age groups 50—54 and 55—59

Both Crevalcore and Montegiorgio show a different set of peculiarities in age distribution — a great shortage of men aged 40—44 and a less marked shortage of men aged 55—59 At Crevalcore the percentages of all men aged

pressure — Crevalcore higher than Montegiorgio which in turn is higher than Nicotera It does not seem however that in these samples there is simply a linear relationship between median blood pressure and median relative weight or body fatness Montegiorgio and Nicotera do not really differ much in relative weight or Σ skinfolds but the difference in blood pressure is significant

Serum cholesterol tends to be lower in Nicotera especially at the older ages than in either of the other villages but the cholesterol values are not high in any of these samples

Compared with the averages of all men in these cooperative studies the men of Crevalcore tend to be relatively heavy fat and characterized by high blood pressures the men of Nicotera are light thin and have low blood pressures and the men of Montegiorgio are intermediate

Full details of the distributions of these variables in these villages are given in the Appendix Cumulative frequency distributions with a probability scale for the ordinate are given in Figures C2 1 C2 2 and C2 3 Because no or only trivial trends with age over the range 40—59 were shown for height Σ skinfolds and serum cholesterol ages 40—59 were combined for these variables The other variables showed clear age trends so in Figs C2 1 C2 2 and C2 3 a distinction is made between ages 40—49 (heavy line) and 50—59 (light line)

Departure from a straight line of the cumulative distributions in Figs C2 1 C2 2 and C2 3 indicates deviation from a normal probability distribution As in other samples in the present series of cooperative studies non normality is most marked for Σ skinfolds but except for height it is evident to at least some degree for the other variables Transformations to make closer approximations to normality can be found for these other variables but these do not have general validity e g a transformation that does nicely for systolic blood pressure at ages 40—49 does less well at ages 50—59 Σ skinfolds requires a different transformation for Crevalcore than for Montegiorgio These facts argue strongly for the use of statistical methods in the analysis of these data that do not assume normal distributions

Physical Activity, Occupation and the Measured Variables

Relationships between these measured variables and physical activity and occupational status may be examined with the data in Tables C2 4—C2 7 inclusive In Nicotera Crevalcore and Montegiorgio relatively few men were sedentary (Activity Class 1) or in the upper socio-economic class of occupations (Code nos 1—13 professional managerial and business-owner classes) And in this latter socio-economic class almost none of the men were engaged in heavy physical activity (Class 3)

In Crevalcore when occupation is ignored the men in Activity Class 1 (sedentary) were compared with the other men more prone to be overweight to elevated blood pressure and much more prone to obesity they did not differ significantly in the tendency to hypercholesterolemia Because larger numbers are concerned a more reliable analysis can be made by comparing men of Activity Class 2 with those in Class 3 The most active men (Class 3) compared with those in Class 2 tend to be less prone to excess body fat slightly less prone to overweight but were not significantly different in regard to blood pressure or serum cholesterol On the other hand when physical activity is ignored the men in Occupational Classes 1—13 in Creval-

TABLE C2 1

Physical activity of men in rural Italy classed by age and habitual physical activity ('ACT ," 1 = sedentary and light 2 = moderate 3 = heavy work) N = total men Table entries are percentages of all men of given age in the area

AGE	NICOTERA N = 570			CREVALCORE, N = 992			MONTEGIORGIO N = 719		
	ACT 1	ACT 2	ACT 3	ACT 1	ACT 2	ACT 3	ACT 1	ACT 2	ACT 3
40-44	--	--	--	13 7	21 7	64 6	4 1	26 8	69 1
45-49	20 4	13 9	65 7	11 6	20 8	67 6	4 0	23 9	72 1
50-54	20 3	13 0	66 7	9 6	18 1	72 3	9 7	20 7	69 6
55-59	34 2	9 4	56 4	13 1	15 4	71 5	9 1	40 9	50 0
40-59	23 7	12 6	63 7	11 7	19 0	69 3	6 7	26 6	66 7

TABLE C2 2

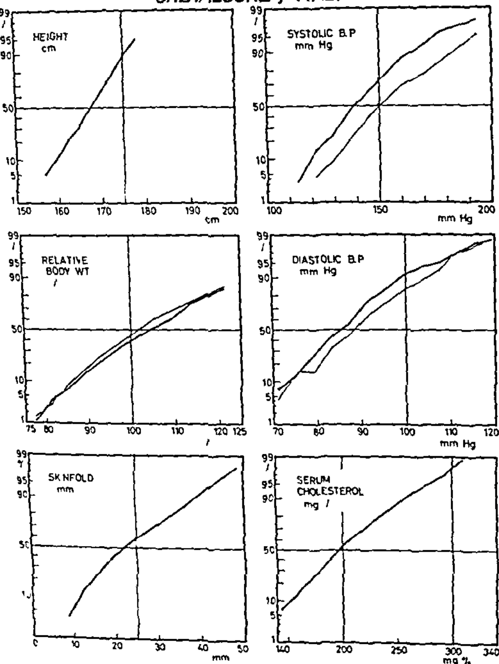
Occupation of men in rural Italy classed Codes 1-15 (business professional business owners and government officials), Codes 66-69 71-75 (farming agriculture and forestry) and all others Table entries are percentages of all men in the area

OCCUPATION	NICOTERA	CREVALCORE	MONTEGIORGIO
Codes 1-15	11 3	6 9	8 5
" 66-69 71-75	50 0	44 1	68 2
All Other	38 7	49 0	23 3

TABLE C2 3

Medians for Italian men classed by age and these values as percentages of the averages of the medians for all 18 samples of men

AREA	VARIABLE	MEDIAN VALUES				MEDIAN % OF AVERAGE			
		40-44	45-49	50-54	55-59	40-44	45-49	50-54	55-59
NICOTERA	Height (cm)	--	162	161	160	--	95 7	95 5	95 3
"	Rel Wt (%)	--	94	89	91	--	97 7	93 5	96 7
"	Σ Skinfolds	--	13	13	14	--	63 7	62 8	70 4
"	Syst B P	--	125	127	136	--	94 0	92 7	96 7
"	Diast B P	--	75	75	78	--	92 1	89 9	92 5
"	Serum Chol	--	184	174	166	--	88 8	83 3	80 3
CREVALCORE	Height (cm)	169	168	168	167	99 5	99 4	99 8	99 6
"	Rel Wt (%)	105	103	102	101	107 0	107 1	107 1	107 3
"	Σ Skinfolds	23	21	22	22	108 5	102 9	106 3	110 6
"	Syst B P	136	142	147	157	103 8	106 8	107 3	111 7
"	Diast B P	84	87	88	90	103 7	106 9	105 5	106 8
"	Serum Chol	194	194	198	204	94 0	93 6	94 8	98 7
MONTEGIORGIO	Height (cm)	165	165	163	162	97 2	97 6	96 9	96 6
"	Rel Wt (%)	99	98	94	94	100 9	93 0	98 7	99 9
"	Σ Skinfolds	15	16	14	14	70 8	78 4	67 6	70 4
"	Syst B P	128	134	137	142	97 7	100 8	100 0	101 0
"	Diast B P	78	80	81	83	96 3	98 3	97 1	98 5
"	Serum Chol	192	200	199	198	93 0	96 5	95 3	95 8



CREVALCORE , ITALY
HEIGHT cm
SYSTOLIC B.P mm Hg
RELATIVE BODY WT
DIASTOLIC B.P mm Hg
SKINFOLD mm
SERUM CHOLESTEROL mg
cm
mm Hg
mm
mg %

Figure C2.2

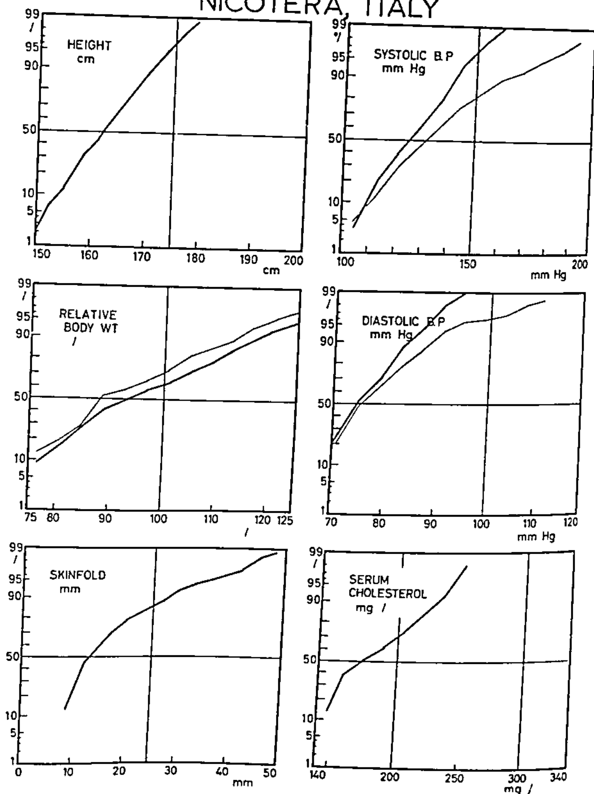

NICOTERA, ITALY
HEIGHT
cm
SYSTOLIC B.P
mm Hg
RELATIVE
BODY WT
/
DIASTOLIC B.P
mm Hg
SKINFOLD
mm
SERUM
CHOLESTEROL
mg /
cm
mm Hg
mm
mg /

Figure C2 1

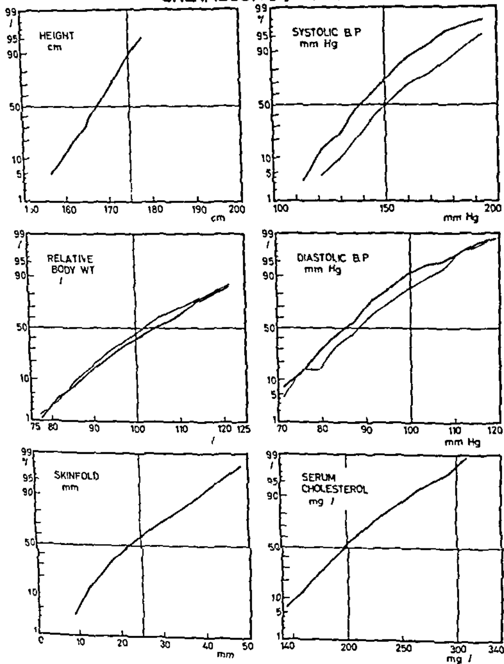

CREVALCORE, ITALY
HEIGHT cm
SYSTOLIC B.P mm Hg
RELATIVE BODY WT %
DIASTOLIC B.P mm Hg
SKINFOLD mm
SERUM CHOLESTEROL mg %

Figure C2 2

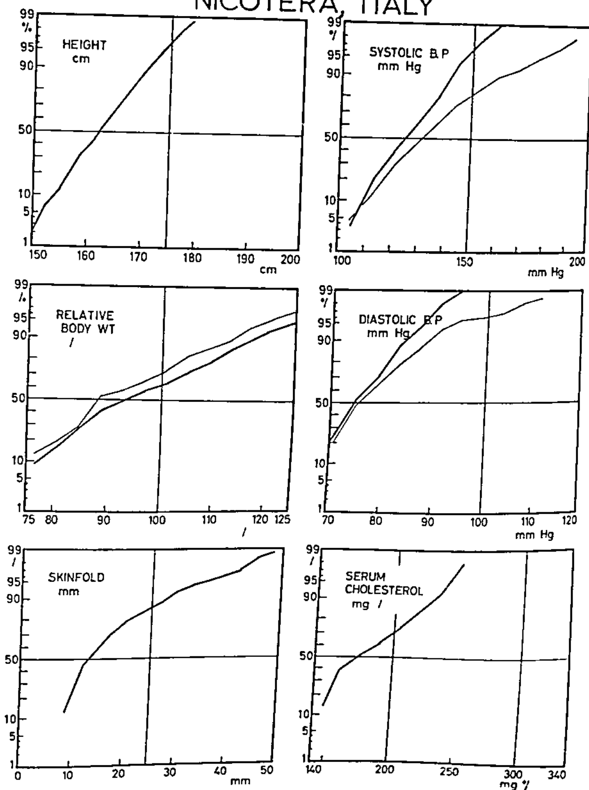

NICOTERA, ITALY
HEIGHT
cm
SYSTOLIC B.P
mm Hg
RELATIVE
BODY WT
%
DIASTOLIC B.P
mm Hg
SKINFOLD
mm
SERUM
CHOLESTEROL
mg %
mm Hg
mg %

Figure C2 1

TABLE C2 4

Occupation and physical activity versus measured variables in Crevalcore and Montegiorgio Numbers of men with "Low" and with "High" values of the variables indicated "Low" and "High" are the bottom 30 and the top 30 per cent respectively, of the distributions of all men of the same age in the same sample

OCCUPATION	PHYSICAL ACTIVITY	RELATIVE WT Low	RELATIVE WT High	Σ SKINFOLDS Low	Σ SKINFOLDS High	SYSTOLIC B P Low	SYSTOLIC B P High	DIASTOLIC B P Low	DIASTOLIC B P High	CHOLESTEROL Low	CHOLESTEROL High
CREVALCORE											
1-13	Class 1	2	5	1	6	2	4	2	4	2	2
"	" 2	7	20	4	25	14	10	11	15	12	19
"	" 3	0	2	0	3	1	2	0	2	2	1
"	All Classes	9	27	5	34	17	16	13	21	16	22
14-94	Class 1	27	32	17	38	27	36	20	32	23	27
"	" 2	40	48	30	45	42	36	38	38	41	43
"	" 3	208	181	238	170	196	196	215	195	199	166
"	All Classes	275	261	285	253	265	268	273	265	263	256
1-94	Class 1	29	37	18	44	29	40	22	36	25	29
"	" 2	47	68	34	70	43	46	49	53	53	62
"	" 3	208	183	238	173	197	198	215	197	201	187
MONTEGIORGIO											
1-13	Class 1	3	4	2	5	1	3	3	3	1	3
"	" 2	9	26	7	26	12	22	8	11	7	24
'	" 3	0	0	0	0	0	0	0	0	0	0
"	All Classes	12	30	9	31	13	25	11	14	8	27
14-94	Class 1	10	8	7	10	5	8	5	7	8	10
"	" 2	33	60	26	61	33	55	38	55	31	52
"	" 3	154	115	172	110	163	125	158	125	163	120
"	All Classes	197	183	205	181	201	188	201	187	202	182
1-94	Class 1	13	12	9	15	6	11	8	10	9	13
"	" 2	42	66	33	87	45	77	46	66	38	76
"	' 3	154	115	172	110	163	125	158	125	163	120

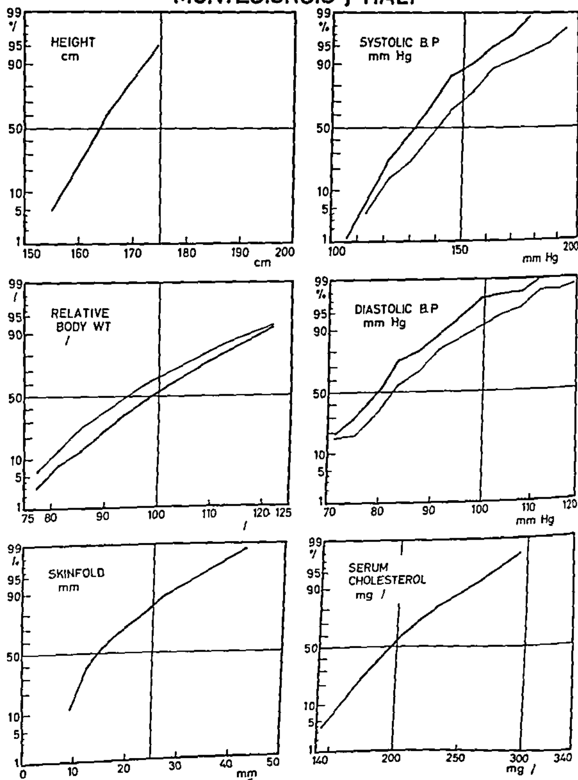

MONTEGIORGIO , ITALY
HEIGHT
cm
SYSTOLIC B.P
mm Hg
RELATIVE
BODY WT
DIASTOLIC B.P
mm Hg
SKINFOLD
mm
SERUM
CHOLESTEROL
mg

Figure C2 3

core were much more prone than the other men to overweight and obesity but were not significantly different in the other variables

In Montegiorgio when Occupational Class is ignored the few men in Activity Class 1 did not differ significantly from the rest of the men in regard to any of the five variables However the men in Activity Class 2 were much more prone to high values in all five variables than the men in Activity Class 3 In the reverse analysis when physical activity is ignored the men in Occupational Classes 1—13 in Montegiorgio tended to be more often in the "high" category of all of the variables and this tendency is statistically significant for all variables except diastolic blood pressure

Because of the correlation between physical activity and occupation in these samples more meaningful results require comparison of physical activity classes within given Occupational Classes and *vice versa* In order to provide larger numbers for this comparison it is useful to combine the Crevalcore and Montegiorgio samples and this seems justifiable because in these respects there are no significant differences between these samples But even if the Crevalcore and Montegiorgio samples are combined Occupational Classes 1—13 contain too few men in either Activity 1 or Activity 3 so these categories are not covered in the following analysis

Within Activity 2 in the combined Crevalcore and Montegiorgio samples the men in the higher socio-economic group differ from the rest of the men significantly in regard to body fatness (Σ skinfolds) Fifty-one of these men were in the top 30 per cent of the skinfolds distribution compared with the chance expectation of 43.5 men (chi-square = 5.28 and p = 0 03) In relative body weight these men tend to be more often overweight also but the difference is of doubtful significance (chi-square = 3 60 p = 0 06) There are no significant differences in the other variables

Within Occupations 14—94 in the combined Crevalcore-Montegiorgio material there is no significant difference between Activity Classes 1 and 2 in regard to the distribution of any of the variables Comparing Class 1 with Class 3 fails to show a significant difference in regard to relative weight systolic blood pressure or serum cholesterol but there are significant differences in obesity and diastolic blood pressure (chi square = 17 03 and = 4.55 respectively with p less than 0 001 and p = 0 03)

Finally in this combined material in Occupations 14—94 the men in Activity Class 2 are more often in the high category for all variables than the men in Activity Class 3 and the difference is significant except for systolic blood pressure where chi square = 2 81 and p = 0 09 The probability values are less than p = 0 001 for relative weight (chi square = 11 63) and Σ skinfolds (chi square = 34 49) for diastolic blood pressure chi square = 3 90 (p = 0 05) and for serum cholesterol chi-square = 6 14 (p = less than 0 02)

The general picture from the Crevalcore Montegiorgio material is that the distribution of the measured variables is related to both activity and to occupational status so that if only one of these characteristics is considered alone its effect on the measured variables is much over-estimated

The clearest association involving physical activity independently from socio-economic status concerns body fatness and it is reasonable to suggest that this is a cause-and-effect relationship The greater the habitual physical activity the less body fat though not necessarily the less relative body weight The men who do the heaviest work obviously tend to have

TABLE C2 5

Activity 1 vs Activity 2 Excess frequency of high values (deciles 8-10) of the variables observed among men of Activity 1, expressed as % of expectation from total numbers of men in Activities 1 plus 2 Also chi-square values for the differences between observed and expected distributions

OCCUPATION	REL WT Excess	Chi^2	Σ SKINFOLDS Excess	Chi^2	SYST B P Excess	Chi^2	DIAST B P Excess	Chi^2	CHOLESTEROL Excess	Chi^2
Nicotera										
1-94	20 8	8 97	25 7	14 80	17 1	3 27	-6 7	0 45	1 4	0
1-13	5 1	0 51	3 9	0 43	10 6	1 79	6 0	0 35	-9 1	0
14-94	36 1	6 85	42 9	8 56	18 9	0 87	-23 1	1 91	0	0
Crevalcore										
1-94	16 4	1 50	13 4	1 47	33 3	6 75	16 1	1 49	-7 1	0 21
1-13	11 1	0	9 1	0	53 8	0 50	14 3	0	-42 9	0 53
14-94	1 6	0	18 8	2 51	27 2	4 54	16 4	1 42	-2 5	0
Montegiorgio										
1-94	-20 0	0 86	-5 1	0 01	-19 1	0 63	-24 8	1 12	-7 8	0 05
1-13	-4 8	0	13 6	0 01	-14 3	0	-11 8	0	-26 8	0 21
14-94	-25 2	0 89	-11 5	0 12	-20 8	0 48	-29 3	1 09	0	0

TABLE C2 6

Activity 2 vs Activity 3 Occupations 14-94 only Excess frequency as in Table C2 5 of high values among men of Activity 2

SAMPLE	REL WT Excess	Chi^2	Σ SKINFOLDS Excess	Chi^2	SYST B P Excess	Chi^2	DIAST B P Excess	Chi^2	CHOLESTEROL Excess	Chi^2
Nicotera	22 0	0 59	25 0	0 85	0 6	0	65 6	9 71	36 4	0 06
Crevalcore	31 1	5 40	27 2	3 71	-4 8	0 07	0	0	70 6	19 34
Montegiorgio	48 6	16 01	56 8	21 42	35 5	8 63	35 5	8 63	32 7	6 92

TABLE C2 7

Occupation 1-13 vs 14-94 Excess frequency as in Table C2 5 of high values among men in Occupations 1-13 expressed as % of expectation from total numbers of men in Occupations 1-13 + 14-94

ACTIVITY	REL WT Excess	Chi^2	Σ SKINFOLDS Excess	Chi^2	SYST B P Excess	Chi^2	DIAST B P Excess	Chi^2	CHOLESTEROL Excess	Chi^2
Nicotera										
1+2	11 5	0 90	26 5	6 35	10 1	0 35	0	0	35 1	0 48
1	-3 1	0 04	4 5	0 19	4 3	0 04	13 9	0 91	21 2	0 04
2	15 4	0	53 8	0 50	-54 6	0 34	-46 0	0 76	150 0	0 05
Crevalcore										
1+2	6 4	0 11	22 5	2 33	-24 7	1 68	1 0	0	1 9	0
1	16 3	0 02	17 6	0 07	-13 0	0	- 4 8	0	37 5	0 25
2	5 3	0 03	29 5	3 13	-19 4	0 54	4 9	0 01	6 7	0 06
Montegiorgio										
1+2	22 4	2 39	27 0	3 55	12 6	0 52	10 6	0 32	26 8	2 79
1	48 1	0 46	47 1	0 80	20 0	0	30 4	0 03	0	0
2	19 3	1 52	16 6	1 13	11 1	0 33	7 7	0 11	30 4	3 15

Probabilities p associated with chi-square values 2 71 p = 0 10 3 84 p - 0 05 5 41 p = 0 02 6 64 p = 0 01 10 83 p = 0 001

core were much more prone than the other men to overweight and obesity but were not significantly different in the other variables

In Montegiorgio when Occupational Class is ignored the few men in Activity Class 1 did not differ significantly from the rest of the men in regard to any of the five variables However the men in Activity Class 2 were much more prone to high values in all five variables than the men in Activity Class 3 In the reverse analysis when physical activity is ignored the men in Occupational Classes 1—13 in Montegiorgio tended to be more often in the "high" category of all of the variables and this tendency is statistically significant for all variables except diastolic blood pressure

Because of the correlation between physical activity and occupation in these samples more meaningful results require comparison of physical activity classes within given Occupational Classes and *vice versa* In order to provide larger numbers for this comparison it is useful to combine the Crevalcore and Montegiorgio samples and this seems justifiable because in these respects there are no significant differences between these samples But even if the Crevalcore and Montegiorgio samples are combined Occupational Classes 1—13 contain too few men in either Activity 1 or Activity 3 so these categories are not covered in the following analysis

Within Activity 2 in the combined Crevalcore and Montegiorgio samples *the men in the higher socio-economic* group differ from the rest of the men significantly in regard to body fatness (Σ skinfolds) Fifty-one of these men were in the top 30 per cent of the skinfolds distribution compared with the chance expectation of 43.5 men (chi-square = 5.28 and p = 0.03) In relative body weight these men tend to be more often overweight also but the difference is of doubtful significance (chi-square = 3.60 p = 0.06) There are no significant differences in the other variables

Within Occupations 14—94 in the combined Crevalcore-Montegiorgio material there is no significant difference between Activity Classes 1 and 2 in regard to the distribution of any of the variables Comparing Class 1 with Class 3 fails to show a significant difference in regard to relative weight systolic blood pressure or serum cholesterol but there are significant differences in obesity and diastolic blood pressure (chi-square = 17.03 and = 4.55 respectively with p less than 0.001 and p = 0.03)

Finally in this combined material in Occupations 14—94 the men in Activity Class 2 are more often in the high category for all variables than the men in Activity Class 3 and the difference is significant except for systolic blood pressure where chi square = 2.81 and p = 0.09 The probability values are less than p = 0.001 for relative weight (chi square = 11.63) and Σ skinfolds (chi-square = 34.49) for diastolic blood pressure chi square = 3.90 (p = 0.05) and for serum cholesterol chi-square = 6.14 (p = less than 0.02)

The general picture from the Crevalcore-Montegiorgio material is that the distribution of the measured variables is related to both activity and to occupational status so that if only one of these characteristics is considered alone its effect on the measured variables is much over-estimated

The clearest association involving *physical activity* independently from *socio-economic status* concerns body fatness and it is reasonable to suggest that *this is a* cause-and effect relationship The greater the habitual physical activity the less body fat though not necessarily the less relative body weight The men who do the heaviest work obviously tend to have

a low fat mass but a high muscle mass It seems also that the men in Activity Class 3 tend to have lower values for blood pressure and serum cholesterol

The group of Occupations 14—94 is far from being homogeneous in socio-economic status it includes very poor men as well as men who are relatively moderately rich it includes men of the lowest social class as well as men of much higher social standing The result then is that this analysis may substantially under-estimate the effect of socio-economic status on the distribution of these variables

Smoking Habits

Cigar and pipe smoking is negligible in Italy particularly in rural areas and cigarette smoking is discouraged by the absence of advertising (by law) and high price Both in Crevalcore and Montegiorgio one-fourth of the men had never smoked and at the time of the examinations non-smokers represented 37 per cent of the men in Crevalcore and 41 per cent in Montegiorgio Men who regularly smoked 20 or more cigarettes a day amounted to 17 8 per cent of men aged 40—59 at Crevalcore and only 9 6 per cent at Montegiorgio Heavy cigarette smoking was even less common in Nicotera but the records made in 1957 are not fully comparable Smoking habit data are given in Tables C2 8 C2 9

As in other samples in this cooperative study the non-smokers at Crevalcore and Montegiorgio tended to be more often overweight and obese than the smokers Among 362 non-smokers at Crevalcore 64 per cent were above and 36 per cent below the median relative body weight for all men aged 40—59 at Crevalcore at Montegiorgio 61 per cent of the non-smokers were above the median relative weight The discrepancy in body fatness was equally striking At Crevalcore 63 per cent of the non-smokers were in the above-median class for Σ skinfolds the corresponding figure for Montegiorgio was 65 per cent

Non-smokers in Crevalcore and Montegiorgio also tended to be in the above-median classes for blood pressure and serum cholesterol but this tendency was less marked than in regard to relative weight and Σ skinfolds The largest trend in these variables was for diastolic blood pressure at Crevalcore where there were 215 non-smokers in the above-median class compared with an expected number of 183 8 the difference has extremely high statistical significance

The tendency to higher serum cholesterol values among all non-smokers than among all smokers is not statistically significant in either village Curiously both in Crevalcore and in Montegiorgio the men who had once smoked but had quit tended to have higher serum cholesterol values than light smokers (1—9 cigarettes per day) For the median cutting point the difference is significant at the level of p = 0 02 (chi-square = 6 09)

Electrocardiographic Findings

Tables C2 10—C2 13 inclusive summarize the electrocardiographic findings in Crevalcore and Montegiorgio Classified by the Minnesota Code the frequency of reportable items in the record taken in rest rises with age in both areas and in each age the prevalence of abnormality (rate per 1000 men) tends to be slightly higher in Crevalcore than in Montegiorgio The most common abnormalities in both areas are left axis deviation (Code II 1) high amplitude R waves left type (Code III 1) sinus tachycardia (Code VIII 7) and small degrees of T wave negativity (Code V 3)

TABLE C2 8

Cigarette smoking habits of men of Italy Percentage of men who never smoked, who had stopped who smoked 1-9 10-19, 20 or more cigarettes daily at the time of their examination

SAMPLE	AGE	NEVER	QUIT	1-9	10-19	20 OR MORE
Nicotera	45-49	18 1	9 7	40 1	22 9	9 2
"	50-54	24 6	9 8	33 7	26 2	5 7
'	55-59	21 7	16 5	35 7	18 3	7 8
'	45-59	20 7	11 4	37 3	22 6	8 0
Crevalcore	40-44	28 1	14 6	14 6	16 5	26 2
"	45-49	23 0	10 5	18 0	29 8	18 7
'	50-54	24 3	12 7	19 2	29 1	14 7
	55-59	27 0	12 6	20 9	26 0	13 5
	40-59	25 1	12 3	18 5	26 5	17 6
Montegiorgio	40-44	22 8	13 8	27 6	24 4	11 4
	45-49	28 0	15 4	27 1	20 2	9 3
	50-54	24 7	14.4	27 4	23 7	9 8
	55 59	26 9	18 5	29 2	17 7	7 7
'	40-59	25 9	15 4	27 7	21 5	9 5

TABLE C2 9

Smoking. Number of men in Italy below (LOW) and above (HIGH) the age specific medians, for age and area, of measured variables, classed according to smoking habits. HEAVY = 20 or more, OTHER = 1-19 cigarettes daily

VARIABLE	SAMPLE	NON-SMOKERS		HEAVY		OTHER	
		LOW	HIGH	LOW	HIGH	LOW	HIGH
Relative Weight	Crevalcore	130	232	96	77	261	179
"	Montegiorgio	115	178	39	29	203	148
ΣSkinfolds	Crevalcore	137	233	96	78	260	183
"	Montegiorgio	113	210	43	25	202	149
Systolic B P	Crevalcore	163	205	86	87	241	196
"	Montegiorgio	143	151	34	34	180	172
Diastolic B. P	Crevalcore	153	215	96	77	239	197
"	Montegiorgio	142	152	31	37	186	166
Serum Cholesterol	Crevalcore	177	185	71	98	231	198
"	Montegiorgio	136	153	38	28	180	171

TABLE C2 10

CREVALCORE ITALY

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code		AGE GROUP (Number of Men) 40-44 (174)	45-49 (303)	50 54 (295)	55 59 (221)
Total with reportable ECG Items	I - IX		64 (367 8)	126 (415 8)	131 (444 1)	117 (529 4)
Q Waves	I	1	0	0	3 (10 2)	2 (9 0)
		2	3 (17 2)	1 (3 3)	2 (6 8)	2 (9 0)
		3	5 (28 7)	7 (23 1)	3 (10 2)	7 (31 7)
Axis Deviation	II					
Left		1	5 (28 7)	11 (36 3)	11 (37 3)	14 (63 3)
Right		2	0	0	0	0
High Amplitude R Waves	III					
Left type		1	9 (51 7)	13 (42 9)	15 (50 8)	18 (81 4)
Right type		2	0	3 (9 9)	0	2 (9 0)
S T Depression (rest)	IV					
S T J 1 mm or more horiz or downward segment		1	0	4 (13 2)	5 (16 9)	6 (27 1)
S T J 0 5 1 mm horiz or downward segment		2	1 (5 7)	6 (19 8)	5 (16 9)	3 (13 6)
No S T J plus segment downward		3	0	0	2 (6 8)	0
S T J 1 mm or more upward segment		4	0	2 (6 6)	5 (16 9)	1 (4 5)
T Wave Negativity (rest)	V					
5 mm or more		1	0	0	0	2 (9 0)
1 mm to 5 mm		2	1 (5 7)	5 (16 5)	5 (16 9)	4 (18 1)
0 + 1 mm		3	8 (46 0)	7 (23 1)	11 (37 3)	12 (54 3)
A V Conduction Defect	VI					
Complete Block		1	0	0	0	0
Partial Block		2	0	0	0	0
P R over 0 21 second		3	1 (5 7)	2 (6 6)	0	0
Accelerated Conduction		4	2 (11 5)	1 (3 3)	1 (3 4)	0
Ventricular Blocks	VII					
Left Bundle		1	0	1 (3 3)	0	2 (9 0)
Right Bundle		2	1 (5 7)	7 (23 1)	2 (6 8)	1 (4 5)
Incompl t Right Bundle		3	0	4 (13 2)	4 (13 6)	3 (13 6)
Intraventricular Block		4	0	0	0	0
Arrhythmias	VIII					
P mature Beats		1	1 (5 7)	0	3 (10 2)	0
V nt icular tachycardia		2	0	0	0	0
At ial fibrillation flutter		3	0	3 (9 9)	0	3 (13 6)
Supra vent tachycardia		4	0	0	0	0
V ntricular rhythm		5	0	0	0	0
A V nodal rhythm		6	0	0	1 (3 4)	1 (4 5)
Sinus tachyc rdia		7	7 (40 2)	13 (42 9)	13 (44 1)	10 (45 2)
Siru bradycardia		8	0	7 (23 1)	2 (6 8)	4 (18 1)
Technically poor records	IX	8	0	2 (6 6)	0	1 (4 5)

TABLE CZ 11

CREVALCORE ITALY

FREQUENCY OF POST-EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1,000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (172)	45-49 (297)	50 54 (289)	55 59 (211)
Exercise tests not made or	X 1				
incomplete	X 2	2 (11 5)	6 (19 8)	6 (20 3)	10 (45 2)
S-T Depression post-exercise (none at rest)	XI				
S-T - J 1 mm or more horiz or downward segment	1	3 (17 4)	1 (3 4)	1 (3 5)	2 (9 5)
S-T - J 0 5 - 1 mm , horiz or downward segment	2	2 (11 6)	3 (10 1)	1 (3 5)	6 (28 4)
No S-T-J plus segment downward	3	0	0	0	1 (4 7)
S-T - J 1 mm or more, upward segment	4	2 (11 6)	5 (16 8)	5 (17 3)	4 (19 0)
T Wave Negativity post-exercise (none at rest)	XII				
-5 mm or more	1	0	0	0	0
-1 to -5 mm	2	0	1 (3 4)	0	1 (4 7)
0 ± 1 mm	3	2 (11 6)	2 (6 7)	2 (6 9)	7 (33 2)
Arrhythmias post-exercise	XV				
(none at rest)	1	2 (11 6)	8 (26 9)	4 (13 8)	7 (33 2)
Technically poor post-exercise records	XI 8	3 (17 4)	6 (20 2)	5 (17 3)	3 (14 2)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

ECG FINDING	ECG Code	40-44	45-49	50 54	55 59
At Rest					
Large Q Waves	I 1	0	0	3 (10 2)	2 (9 0)
Lesser Q Waves with Negative T Waves	I 2,3 + V 1 2	0	1 (3 3)	1 (3 4)	1 (4 5)
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	4 (23 0)	4 (13 2)	6 (20 3)	4 (18 1)
S-T Depression as sole anomaly	IV 1-4 only	0	1 (3 3)	0	0
High Amplitude R with S-T Depression	III 1+ IV 1-4	0	5 (16 5)	4 (13 6)	4 (18 1)
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1, 2 4	1 (5 7)	8 (26 4)	2 (6 8)	3 (13 6)
Arrhythmias	VIII 2-6	0	3 (9 9)	1 (3 4)	4 (18 1)
Post exercise					
S-T Depression as sole anomaly	XI 1-4 only	4 (23 3)	7 (23 6)	0	5 (23 7)
Negative T as sole anomaly	XII 1-3 only	0	2 (6 7)	1 (3 5)	0
Ventricular Conduction Defect as sole anomaly	XIV 1 2 4 only	0	0	0	0
Arrhythmias as sole anomaly	XV 1 only	2 (11 6)	5 (16 8)	2 (6 9)	3 (14 2)

TABLE C2 12

MONTEGIORGIO ITALY

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40 44 (123)	45 49 (247)	50 54 (217)	55 59 (130)
Total with reportable ECG Items	I IX	42 (341 5)	99 (400 8)	96 (442 4)	61 (469 2)
Q Waves	I 1	0	1 (4 0)	2 (9 2)	1 (7 7)
	2	1 (8 1)	0	3 (13 8)	2 (15 4)
	3	0	3 (12 1)	0	2 (15 4)
Axis Deviation	II				
Left	1	3 (24 4)	13 (52 6)	16 (73 7)	12 (92 3)
Right	2	0	0	0	0
High Amplitude R Waves	III				
Left type	1	6 (48 8)	3 (12 1)	12 (55 3)	3 (23 1)
Right type	2	0	0	0	0
S T Depression (rest)	IV				
S T J 1 mm or more horiz or downward segment	1	1 (8 1)	1 (4 0)	2 (9 2)	1 (7 7)
S T J 0 5 1 mm horiz or downward segment	2	1 (8 1)	1 (4 0)	2 (9 2)	2 (15 4)
No S T J plus segment downward	3	0	1 (4 0)	0	1 (7 7)
S T J 1 mm or more upward segment	4	0	1 (4 0)	1 (4 6)	3 (23 1)
T Wave Negativity (rest)	V				
5 mm or more	1	1 (8 1)	1 (4 0)	0	0
1 mm to 5 mm	2	1 (8 1)	1 (4 0)	4 (18 4)	0
0 ± 1 mm.	3	1 (8 1)	7 (28 3)	7 (32 3)	4 (30 8)
A V Conduction Defect	VI				
Complete Block	1	0	0	0	0
Partial Block	2	0	0	0	0
P R over 0 21 second	3	1 (8 1)	3 (12 1)	1 (4 6)	0
Accelerated Conduction	4	0	0	0	1 (7 7)
Ventricular Blocks	VII				
Left Bundle	1	0	0	0	1 (7 7)
Right Bundle	-	0	1 (4 0)	2 (9 2)	0
Incomplete Right Bundle	3	1 (8 1)	5 (20 2)	1 (4 6)	4 (30 8)
Intraventricular Block	4	0	0	1 (4 6)	0
Arrhythmias	VIII				
Premature Beats	1	1 (8 1)	0	5 (23 0)	1 (7 7)
Ventricular tachycardia	2	0	0	0	0
Atrial fibrillation flutter	3	0	0	1 (4 6)	1 (7 7)
Supra vent tachycardia	4	0	0	0	0
Ventricular rhythm	5	0	0	0	0
A V nodal rhythm	6	1 (8 1)	1 (4 0)	1 (4 6)	0
Sinus tachycardia	7	4 (32 5)	9 (36 4)	3 (13 8)	4 (30 8)
Sinus bradycardia	8	2 (16 3)	5 (20 2)	5 (23 0)	4 (30 8)
Technically poor records	IX 8	1 (8 1)	1 (4 0)	0	1 (7 7)

TABLE C2 13

MONTEGIORGIO ITALY

FREQUENCY OF POST-EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1,000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (122)	45-49 (241)	50-54 (211)	55 59 (126)
Exercise tests not made or	X 1				
incomplete	X 2	1 (8 1)	6 (24 3)	6 (27 6)	4 (30 8)
S-T Depression post-exercise (none at rest)	XI				
S-T - J 1 mm or more, horiz or downward segment	1	1 (8 2)	2 (8 3)	1 (4 7)	1 (7 9)
S-T - J 0 5 - 1 mm horiz or downward segment	2	2 (16 4)	4 (16 6)	4 (19 0)	2 (15 9)
No S-T-J plus segment downward	3	0	0	1 (4 7)	0
S-T - J 1 mm or more upward segment	4	5 (41 0)	4 (16 6)	7 (33 2)	2 (15 9)
T Wave Negativity post-exercise (none at rest)	XII				
-5 mm or more	1	0	0	0	0
-1 to -5 mm	2	0	0	0	0
0 ± 1 mm	3	1 (8 2)	4 (16 6)	3 (14 2)	1 (7 9)
Arrhythmias post-exercise (none at rest)	XV 1	2 (16 4)	2 (8 3)	5 (23 7)	5 (39 7)
Technically poor post-exercise records	XI 8	2 (16 4)	6 (24 9)	5 (23 7)	4 (31 7)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

At Rest					
Large Q Waves	I 1	0	1 (4 0)	2 (9 2)	1 (7 7)
Lesser Q Waves with Negative T Waves	I 2 3 + V 1 2	1 (8 1)	0	0	0
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	0	1 (4 0)	2 (9 2)	0
S-T Depression as sole anomaly	IV 1-4 only	0	1 (4 0)	0	3 (23 1)
High Amplitude R with S-T Depression	III 1 + IV 1-4	1 (8 1)	0	2 (9 2)	0
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2 4	0	1 (4 0)	3 (13 8)	1 (7 7)
Arrhythmias	VIII 2-6	1 (8 1)	1 (4 0)	2 (9 2)	1 (7 7)
Post-exercise					
S-T Depression as sole anomaly	XI 1-4 only	5 (41 0)	7 (29 0)	5 (23 7)	3 (23 8)
Negative T as sole anomaly	XII 1-3 only	0	3 (12 4)	0	0
Ventricular Conduction Defect as sole anomaly	XIV 1, 2 4 only	0	0	0	0
Arrhythmias as sole anomaly	XV 1 only	2 (16 4)	0	2 (9 5)	3 (23 8)

Electrocardiograms were recorded after the standard exercise test in 700 out of 717 men at Montegiorgio and in 969 out of 993 men at Crevalcore At Montegiorgio the exercise test yielded 18 cases of S-T depression (Code XI 1 2 3) where none had been present at rest thus more than doubling the frequency of this abnormality At Crevalcore the exercise added 20 additional S T depressions to the 32 cases where this abnormality had been present in rest The exercise test was less effective in producing new T wave negativity For Code XII 1 2 exercise produced no new cases at Montegiorgio and only 2 at Crevalcore in rest this abnormality was found in 8 men at Montegiorgio and in 17 men at Crevalcore

The rarity of certain ECG abnormalities is notable in this material — — in a total of 1710 men aged 40—59 there were no cases of complete A-V block only 4 cases of left bundle branch block only 8 cases of auricular fibrillation or flutter If we take major Q waves (Code I 1) as the most definite evidence of previous infarction it is interesting that only 9 cases were found or a rate of 5 3 per thousand men aged 40—59

The Minnesota Code for the ECG was not available until several years after the Nicotera survey Further the ECG records from Nicotera may not be entirely comparable with the ECG records from the other samples because of some questions about technique and equipment However the following may be noted Two farmers aged 55 and 57 and one hairdresser aged 46 had records indicating old infarction (Minnesota Code I 1) Isolated S-T depression of 0 5 mm or more in rest was observed in 9 men (3 aged 45—49 2 aged 50—54 4 aged 54—59) Isolated flat or negative T wave in rest was observed in 5 men (2 aged 45—49 2 aged 50—54 one aged 56) S-T depression associated with T wave abnormality or auricular brillation was noted in 3 men in rest (ages 45 47 54) and 4 men post exercise (ages 49 52 55 59) one of whom was diabetic There were no cases of bundle branch block

Angina pectoris was diagnosed in only one man at Nicotera an obese landowner aged 57 whose ECG was normal Three hypertensive men (B P 160/95 or more) showed ECG evidence of left ventricular hypertrophy their ages were 54 56 and 58 At Nicotera there were five men with rheumatic heart disease (4 aged 45—49 one aged 55) and three with pulmonary heart disease (ages 49 56 and 59) In general then it seems that the prevalence of coronary heart disease at Nicotera was low

Prevalence of Hypertension

The prevalence of hypertension by two different criteria of diastolic blood pressure in these Italian villages is summarized in Table C2 14 Among men of the same age at Crevalcore hypertension was about twice as common as at Montegiorgio and some five times more common than at Nicotera These differences are statistically highly significant For example even the smallest difference that between Montegiorgio and Nicotera with 100 mm in diastole as the criterion proves to have a value of $p < 0\ 02$

In comparison with the average prevalence of hypertension in all 18 samples in these cooperative studies Nicotera is extremely low Montegiorgio is definitely low and Crevalcore is higher than the average All of these differences between Montegiorgio and Nicotera and the rest of the 17 samples are statistically highly significant The difference between Crevalcore and the rest of the populations is not significant

TABLE C2 14

Prevalence of diastolic hypertension (95 or more, 100 or more mm Hg, fifth phase) among men classed by age Percentage of men in rural Italy who are hypertensive compared with the average for all 18 samples of men

SAMPLE	40-44		45-49		50-54		55 59	
	95mm	100mm	95mm	100mm	95mm	100mm	95mm	100mm
Nicotera	--	--	1 3	0 9	4 9	3 3	6 0	4 3
Crevalcore	16 5	8 5	20 5	10 3	25 9	15 5	28 5	17 1
Montegiorgio	5 7	2 4	8 9	2 8	14 7	8 3	15 3	8 4
Mean, 18 samples	13 6	7 9	15 6	8 9	20 9	13 5	21 5	13 8

with 100 mm in diastole as the criterion ($p =$ about 0 12) but with 95 mm as the criterion the difference is highly significant ($p =$ about 0 005)

Prevalence of Overweight

Table C2 15 shows the percentage of men classed by age who were overweight by either of two criteria — 110 per cent or more or 120 per cent or more of the average weight for height and age as given in the Appendix By either criterion overweight was much more common in Crevalcore than in either Nicotera or Montegiorgio The difference between Nicotera and Montegiorgio in this respect is small

Compared with all 17 other samples of men Nicotera differs little Montegiorgio tends to have rather more cases of overweight than expected in Crevalcore the frequency of overweight is about double the expectation

Hypertension versus Other Variables

The distributions of the hypertensive men according to decile classes of relative body weight Σ skinfolds and serum cholesterol concentration are shown in Figures C2 4 C2 5 and C2 6

In all areas the prevalence rate of hypertension rises markedly though not uniformly with increasing values for these other variables absence of a trend would be indicated by random variations about a horizontal straight line At Montegiorgio the upward trend of prevalence with increasing relative weight and with Σ skinfolds seems to be definitely curvilinear This is scarcely indicated at Crevalcore except perhaps in the sharp rise in prevalence from the ninth to the tenth decile in relative body weight

The trend toward increasing prevalence of hypertension with increasing serum cholesterol values seems to be more or less linear in both areas The relationship of hypertension frequency to serum cholesterol is statistically highly significant and the same is true for the relationships to relative weight and Σ skinfolds

These relationships are particularly striking if the prevalence of hypertension in the upper 30 per cent (deciles 8 9 10) of the distributions is expressed as percentage of the prevalence among men in the bottom 30 per cent (deciles 1 2 3) of the distributions For Crevalcore and Montegiorgio combined the percentage is 251 per cent for relative weight 229 per cent for Σ skinfolds 186 per cent for serum cholesterol

The relative rarity at Nicotera of hypertension as here defined and the small numbers on whom serum cholesterol was measured makes the corresponding analysis less certain for that sample However 11 out of a total of 16 "hypertensives" were in the top 3 deciles of relative body weight none in the bottom 3 deciles and 10 out of the 16 were in the top 3 deciles of Σ skinfolds and only one in the bottom 30 per cent of the Σ skinfolds distribution There were only 2 cases of hypertension among the 68 men aged 45—59 on whom cholesterol values were obtained they were both in the eighth decile of the cholesterol distribution of the 68 Nicotera men

Overweight versus Other Variables

If 110 per cent of standard average body weight for given height and age is taken as the criterion for overweight among men aged 40—59 at Crevalcore 34 per cent and at Montegiorgio 20 per cent would be classed as overweight The difference is statistically highly

TABLE C2 14

Prevalence of diastolic hypertension (95 or more, 100 or more mm Hg fifth phase) among men classed by age Percentage of men in rural Italy who are hypertensive compared with the average for all 18 samples of men

SAMPLE	40-44		45-49		50-54		55 59	
	95mm	100mm	95mm	100mm	95mm	100mm	95mm	100mm
Nicotera	--	--	1 3	0 9	4 9	3 3	6 0	4 3
Crevalcore	16 5	8 5	20 5	10 3	25 9	15 5	28 5	17 1
Montegiorgio	5 7	2 4	8 9	2 8	14 7	8 3	15 3	8 4
Mean 18 samples	13 6	7 9	15 6	8 9	20 9	13 5	21 5	13 8

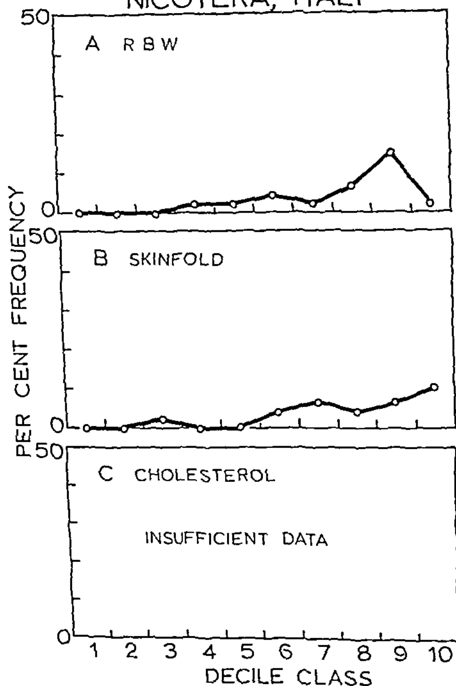

NICOTERA, ITALY
A RBW
B SKINFOLD
C CHOLESTEROL
INSUFFICIENT DATA
PER CENT FREQUENCY
50
0
50
0
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

Figure C2 4

TABLE C2 15

Prevalence of overweight (110 or more and 120 or more per cent of "standard" average for height and age) Percentage of men in rural Italy, classed by age who are overweight compared with the average for all 18 samples of men

SAMPLE	40-44		45-49		50-54		55-59	
	110%	120%	110%	120%	110%	120%	110%	120%
Nicotera	--	--	21 7	9 1	12 2	5 7	17 1	4 3
Crevalcore	42 9	20 9	34 7	16 2	30 1	12 6	33 3	19 1
Montegiorgio	22 0	6 5	24 8	11 8	16 6	6 5	18 5	10 8
Mean 18 samples	*20 9*	*8 4*	*19 4*	*6 9*	*18 1*	*6 7*	*16 8*	*7 3*

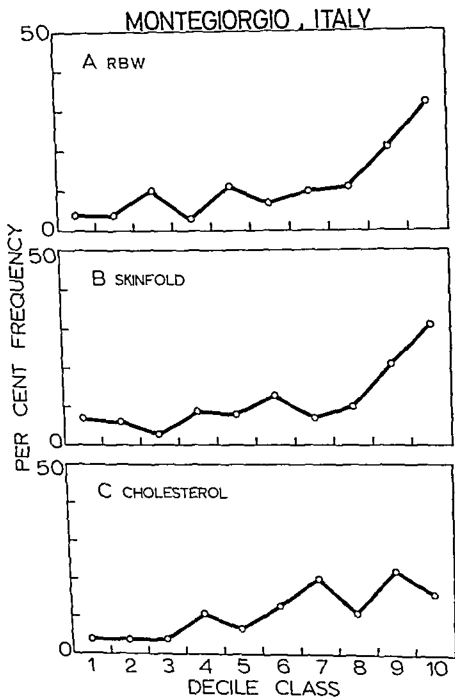

MONTEGIORGIO, ITALY
50
0
A RBW
50
0
B SKINFOLD
50
0
C CHOLESTEROL
PER CENT FREQUENCY
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

Figure C2 6

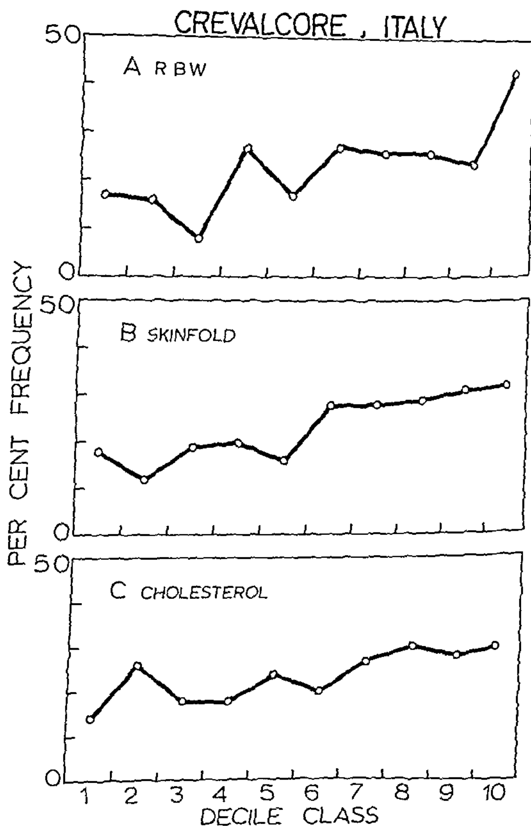
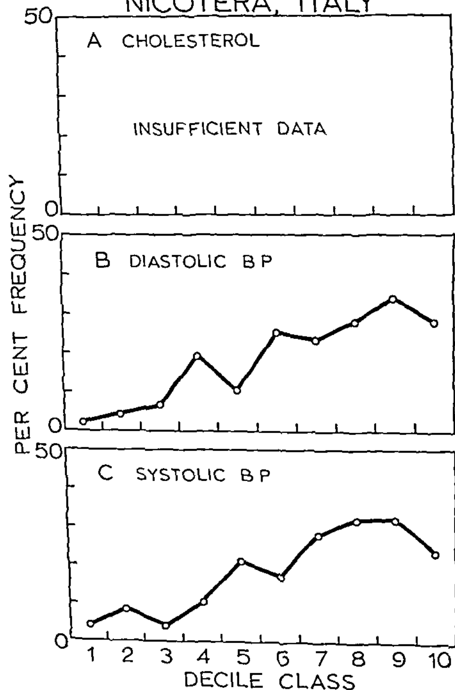

CREVALCORE , ITALY
A RBW
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
50
0
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

Figure C2 5


NICOTERA, ITALY
A CHOLESTEROL
INSUFFICIENT DATA
B DIASTOLIC BP
C SYSTOLIC BP
PER CENT FREQUENCY
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

significant The distribution of these overweight men by decile classes of serum cholesterol, diastolic blood pressure and systolic blood pressure are shown in Figures C2 7 C2 8 and C2 9 In both areas there is a marked tendency for prevalence of overweight to rise with increasing levels of these other variables and in all cases this is of high statistical significance In Crevalcore the trend lines do not depart significantly from a straight line in Montegiorgio there is a distinct suggestion of curvilinearity

As in the case of hypertension it is interesting to compare the prevalence of overweight among the men in the top and the bottom 30 per cent classes of distribution of the other variables For serum cholesterol the prevalence of overweight in the top 30 per cent is 185 per cent of that in the bottom 30 per cent the corresponding figures for systolic and diastolic blood pressures are respectively 205 and 182 per cent

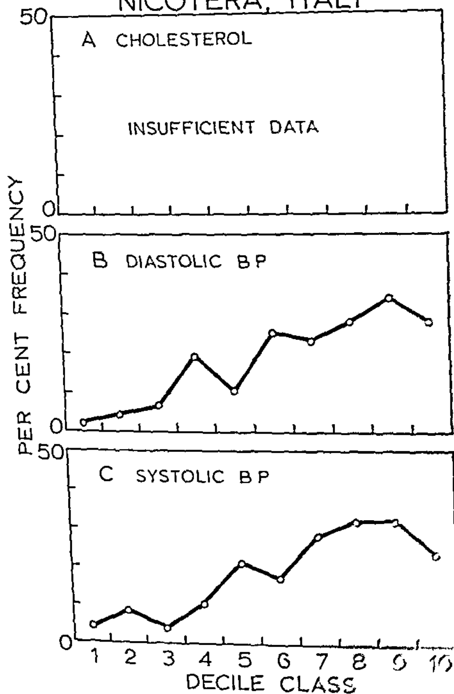
Among 470 Nicotera men aged 45—49 85 men or 18 per cent were classed as overweight by the present criterion The difference from the figure for Montegiorgio is not significant The distribution of these overweight men into the decile classes of blood pressure is shown in Figure C2 7 Forty-one of these overweight men were in the top 30 per cent and only eight in the bottom 30 per cent of the systolic blood pressure distribution The corresponding figures for diastolic blood pressure are 42 men in the top and six men in the bottom 30 per cent Cholesterol data were available on only 13 overweight men eight of them were in the top and one in the bottom 30 per cent of the cholesterol distribution

Prevalence of Obesity and of Hypercholesterolemia

Section H below presents a system for classifying men aged 40—59 into grades of body fatness and of hypercholesterolemia based on the distributions of Σ skinfolds and of serum cholesterol concentration observed in seven samples of men in areas of favorable mortality from all causes and prevalence of coronary heart disease For each of the two variables cutting points were found which include the top 5 10 15 and 20 per cents of the reference population Accordingly Grade 1 obesity is assigned to men whose Σ skinfolds value exceeds 37 mm Grade 2 covers the range 32—37 Grade 3 covers 29—31 and Grade 4 covers 26—28 mm Grade 1 may be considered to be "extreme" The grades of hypercholesterolemia were assigned to serum cholesterol values on a similar basis

With these criteria the prevalence of any degree of obesity proves to be 16 39 and 16 per cent for men at Nicotera Crevalcore and Montegiorgio respectively These figures emphasize the marked contrast between Crevalcore on the one hand and Nicotera and Montegiorgio on the other Further it is clear that obesity is much more common in Crevalcore than the general prevalence in areas of favorable mortality and prevalence of coronary heart disease In Crevalcore 39 per cent of the men are obese but for all areas used as the base only 18 per cent are obese for extreme obesity the corresponding figures are 13 and 5 per cent

The prevalence of hypercholesterolemia of any degree was 22 21 and 12



NICOTERA, ITALY
PER CENT FREQUENCY
50
0
A CHOLESTEROL
INSUFFICIENT DATA
50
0
B DIASTOLIC B P
50
0
C SYSTOLIC B P
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

Figure C2 7

significant The distribution of these overweight men by decile classes of serum cholesterol, diastolic blood pressure and systolic blood pressure are shown in Figures C2 7, C2 8 and C2 9 In both areas there is a marked tendency for prevalence of overweight to rise with increasing levels of these other variables and in all cases this is of high statistical significance In Crevalcore the trend lines do not depart significantly from a straight line in Montegiorgio there is a distinct suggestion of curvilinearity

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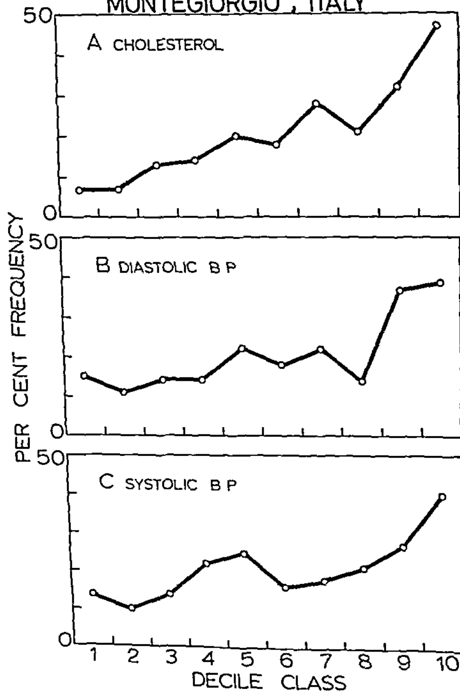


1O.TEGIO(IO; Prevalence o' O ERWEIGHT vs A-cholesterol, B-diastolic, C-systolic blood pressure

10

Figure C2 9

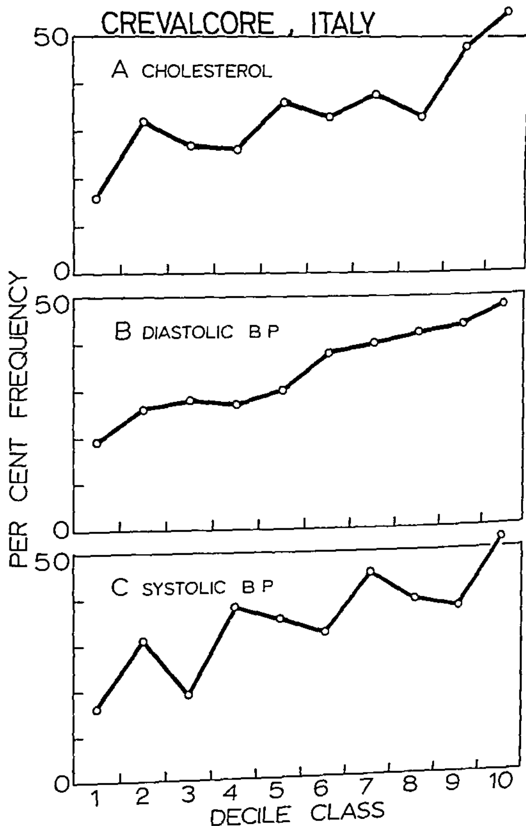
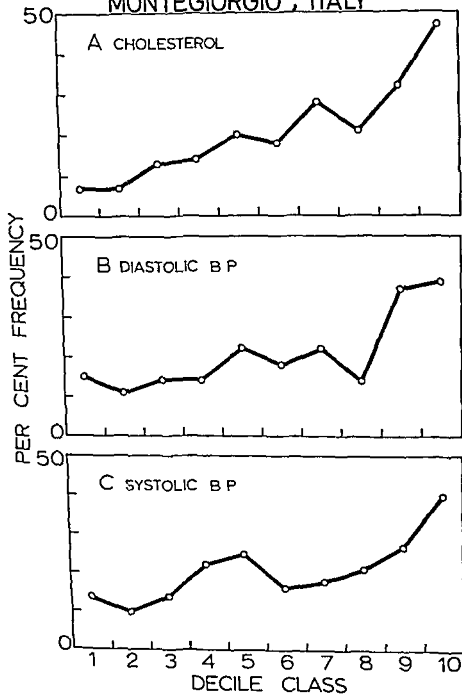

CREVALCORE, ITALY
A CHOLESTEROL
B DIASTOLIC B P
C SYSTOLIC B P
PER CENT FREQUENCY
50
0
50
0
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

Figure C2 8



MONTEGIORGIO, ITALY
A CHOLESTEROL
B DIASTOLIC B P
C SYSTOLIC B P
PER CENT FREQUENCY
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

Figure C2 9

per cent at Crevalcore Montegiorgio and Nicotera respectively the corresponding figures for extreme (Grade 1) hypercholesterolemia are 6 6 and zero per cent

Summary

Over 98 per cent of all men aged 40—59 were examined in three rural areas of Italy centered on the villages of Nicotera (near the "toe" of Italy), Crevalcore (in the lower Po valley) and Montegiorgio (in the hills near the Adriatic Sea in the Province of Marche) In all three areas most of the men were engaged in small-scale farming and there was no other significant industry Correspondingly about two thirds of the men including the oldest group (55—59) habitually did heavy physical work and there were few sedentary men

The men of Nicotera tended to be the shortest and thinnest and to be least often hypertensive the men of Crevalcore being at the opposite extreme in these variables Serum cholesterol concentration tended to be relatively low in all areas but especially so in Nicotera Within each area the least active men tended to be the fattest and to have higher blood pressures and *serum cholesterol values But it is* shown that these relationships are confounded with socio-economic status If either physical activity or socio-economic status is considered alone its apparent effect on the measured variables is much over-estimated

Most of the middle-aged men in these villages smoke cigarettes but relatively few smoke 20 or more cigarettes daily The non-smokers both those who never smoked and those who had stopped were more often overweight and obese than the smokers They also tended to higher blood pressure and serum cholesterol values *but this* was less marked than their trend to relative obesity

Twelve-lead electrocardiograms in rest and after a standard exercise test showed relatively few abnormalities in any of the three areas By any criterion the prevalence of heart disease was low

Hypertension was frequent in Crevalcore and fairly common in Montegiorgio With the criterion of 95 mm or more in diastole (fifth phase) in rest 23 per cent of the men of Crevalcore were hypertensive the corresponding figure for Montegiorgio being 11 per cent Hypertension was uncommon in Nicotera

In all areas the prevalence of hypertension was directly, but curvilinearly related to relative body weight and body fatness there was a less marked apparently linear relationship between serum cholesterol and hypertension Overweight was common in Crevalcore and rare in Nicotera

Acknowledgments

Among the large number of people who made this program possible first thanks are due to the professional staff who helped so much in the field Drs Ratko Buzina (Zagreb) Henry Blackburn (Minneapolis) L A Cioffi *(Naples) Domenico Cotrone* (Rome) Louise Dalderup (Amsterdam) Bruno Imbimbo *(Naples) Aubrey Kagan (Geneva then of* London) Mario Mancini (Naples) Ivan Mohaček (Zagreb) and Sven Punsar (Helsinki) *Some aspects* of the work were aided by Drs J Carlotti (Paris) Martti J Karvonen (Helsinki) Prof Noboru Kimura (Kurume Japan) Mrs Margaret H Keys (Minneapolis) Drs Arrigo Poppi (Verona) Traian Sofonea (Trieste) and Paul Dudley White (Boston)

We are grateful for the excellent cooperation given by the officials and physicians in the villages of Nicotera Crevalcore and Montegiorgio Prof Gino Bergami gave encouragement and made available the facilities of the Istituto di Fisiologia of the University of Naples which served as the 'home base for the field work in Italy

C3 RURAL MEN IN DALMATIA AND SLAVONIA, YUGOSLAVIA

by Ratko Buzina (Zagreb) Ancel Keys (Minneapolis) Ivan Mohaček (Zagreb) Arpad Hahn (Zagreb) Josef Brozek (Lehigh Pennsylvania) and Henry Blackburn (Minneapolis)

Interesting contrasts between villages in Dalmatia and in Slavonia Yugoslavia in regard to the diet and serum cholesterol concentration and reputed differences between those regions in the frequency of heart disease emerged from surveys conducted by several of the present collaborators (Brozek 1955 Brozek et al 1957) These facts plus the experience of excellent cooperation in these areas led to the organization of a more systematic study on a larger scale

Two regions in Dalmatia and in Slavonia were selected on the basis of previous experience and exploratory talks with officials and influential people in the areas of interest Rosters of all men aged 40—59 were established and checked and the work of examination was carried out in the fall of 1958 In Dalmatia 727 out of 742 men in the roster were examined in full (98 0 per cent) and the coverage was also good in Slavonia 749 out of 815 men (91 9 per cent) were examined most of those missed were not refusals but were men who were temporarily at work away from their villages The methods and criteria improved from those developed in the exploratory studies in 1957 in Nicotera and Crete were those that subsequently formed the common protocol of the surveys in Finland and elsewhere and are reported in part in the present publication

Dalmatia

Dalmatia was invaded and long ruled by the Romans who however did not settle there in large numbers The original Illyrian population was displaced by or absorbed into the Slavic population who migrated into the region about fourteen hundred years ago

The area of study comprises a series of villages in a coastal strip of rather barren mountainside along the Adriatic stretching south some 60 kilometers from the port town of Makarska The population is Croatian with here and there notable influences from neighboring Italy Though the region was long ruled by Austria there is little evidence of Germanic or Teutonic influence

Small-scale hand farming provides a livelihood for most of the population with fishing a poor second in importance The land is poor and in the absence of any other industry the econom-

ic level is low Tourist traffic on the Dalmatian coast is increasingly important in the past few years but as yet has had little impact on the villages of the present study The climate is generally mild and temperate Local produce includes grapes wine figs olives, a variety of other fruits and small plots of land devoted to cereals Olive oil has been an important part of the local diet There is a health center and small hospital at Makarska

Slavonia

The area of study in Slavonia is centered in the large village of Dalj near the Drava River in a broad plain close to the Hungarian frontier of Yugoslavia There is bus and local train communication with the nearby regional capital of Osijek which has high schools technical training schools and a general hospital The population is almost entirely Slav about two-thirds Serbs and one-third Croats

This is an agricultural region of flat fertile land well suited to mechanized farming and modern methods are slowly replacing primitive methods of agriculture There is no other industry Economically the population may be somewhat better off than that of Dalmatia, but the full potential of the region has not yet been developed The climate is mid-continental with hot dry summers and severe winters with heavy snows

Distribution by Physical Activity and Occupation

Table C3 1 shows the distribution of the men in Dalmatia and Slavonia In both areas the majority of the men do hard physical work (Grade 3) and there is no tendency for the percentage of men in the high activity class to decline with age over the ages 40—60 there is actually some trend in the opposite direction In Dalmatia only 7 9 per cent of the men 40—59 are sedentary or engaged only in light work This class of physical activity has a larger representation in Slavonia but still amounts only to 17 2 per cent

Table C3 2 summarizes the occupational distribution of these men Only 5 3 per cent in Dalmatia and 8 6 in Slavonia are in the professional managerial and official class and more than half in both areas are simple farmers Ir Dalmatia 13 3 per cent are fishermen but they also do some farming

Distribution by Six Measured Variables

Table C3 3 gives the medians and those medians expressed as percentages of the averages of the medians for all men in the 18 samples in the present cooperative studies of height relative body weight (as percentage of the "standard" average for height and age) body fatness (Σ skinfolds over the triceps muscle and over the tip of the scapula) systolic and diastolic (5th phase) blood pressure, and serum cholesterol concentration Cumulative frequency distributions of these variables are shown in Figures C3 1 and C3 2 Details of the distributions are tabulated in the Appendix

The Dalmatians average about 5 cm taller than the Slavonians and in both samples as in other samples over these ages the youngest men are the tallest In relative body weight the men are similar in both samples and are definitely lighter for their height and age than the general average of the men studied In both areas the men are decidedly thin with all median values being close to 15 mm for Σ skinfolds Allowing for true skin thickness this means that the average thickness of the

TABLE C3 1

Physical activity men in Dalmatia and Slavonia classed by age and physical activity (ACT ' 1 = sedentary and light 2 = moderate 3 = heavy work) N = total men Table entries are percentages of all men of given age in the area

AGE	DALMATIA N = 671			SLAVONIA N = 699		
	ACT 1	ACT 2	ACT 3	ACT 1	ACT 2	ACT 3
40-44	10 6	16 5	72 9	21 6	14 7	63 7
45-49	8 7	15 3	76 0	21 4	8 3	70 3
50-54	6 2	8 1	85 7	11 1	9 1	79 8
55-59	7 8	10 4	81 8	17 1	7 4	75 5
40-59	7 9	11 8	80 3	17 2	9 2	73 6

TABLE C3 2

Occupation of men in Dalmatia and Slavonia classed Codes 1-15 (business professional government officials) Codes 66-69 71-75 (farming agriculture forestry) and all others Table entries are percentages of all men in the area

OCCUPATION	DALMATIA	SLAVONIA
Codes 1-15	5 3	8 6
66-69 71-75	61 4	57 1
All Other	33 3	34 3

TABLE C3 3

Medians for men classed by age in Dalmatia and in Slavonia and these values as percentages of the average of the medians for all 18 samples of men

AREA	VARIABLE	MEDIAN VALUES				MEDIAN % OF AVERAGE			
		40-44	45-49	50-54	55-59	40-44	45 49	50 54	55-59
DALMATIA	Height (cm)	175	173	173	172	103 1	102 3	102 8	102 6
	Rel Wt (*)	94	93	90	88	95 8	96 7	94 5	93 5
	Σ Skinfolds	15	15	14	13	70 8	73 5	67 6	65 3
	Syst B P	136	135	137	135	103 8	101 5	100 0	96 0
	Diast B P	85	80	82	82	104 9	98 3	98 3	97 3
	Serum Chol	182	185	186	188	88 2	89 2	89 0	91 0
SLAVONIA	Height (cm)	170	168	166	168	100 1	99 4	98 6	100 2
	Rel Wt (*)	95	94	88	91	96 8	97 7	92 4	96 7
	Σ Skinfolds	15	15	13	14	70 8	73 5	62 8	70 4
	Syst B P	130	130	131	140	99 2	97 7	95 6	99 6
	Diast B P	79	80	80	84	97 5	98 3	95 9	99 6
	Serum Chol	196	197	200	194	95 0	95 0	95 7	93 9

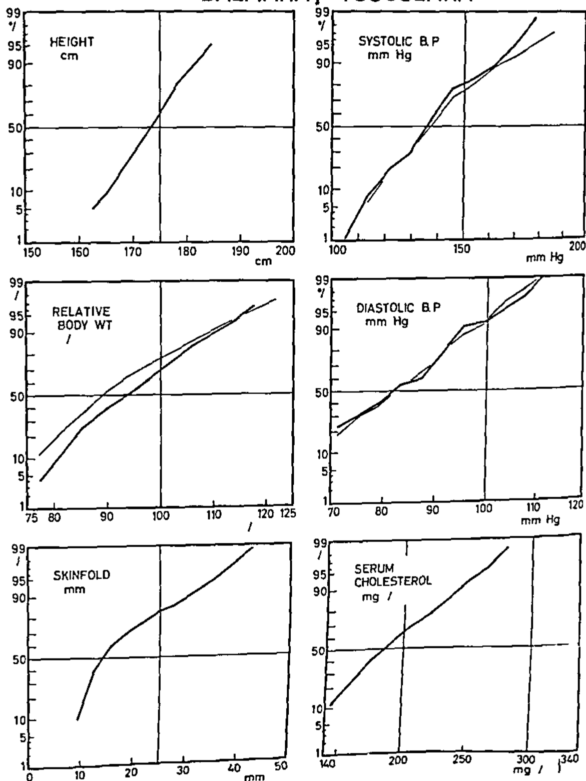

DALMATIA, YUGOSLAVIA
HEIGHT
cm
SYSTOLIC B.P
mm Hg
RELATIVE
BODY WT
DIASTOLIC B.P
mm Hg
SKINFOLD
mm
SERUM
CHOLESTEROL
mg
cm
mm Hg
mm Hg
mm
mg

Figure C3 1

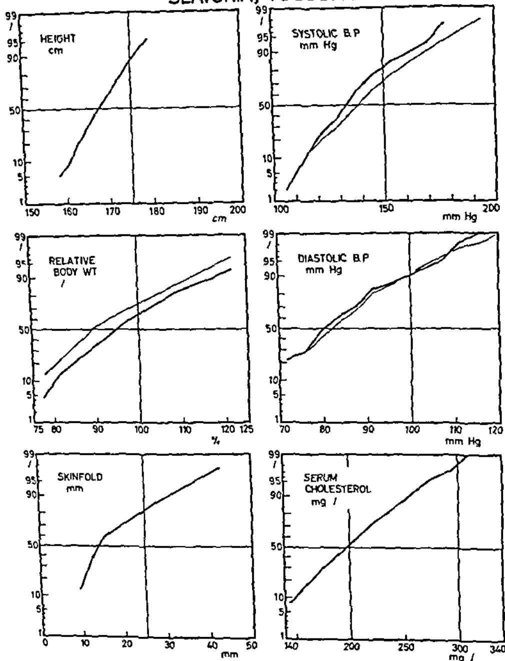
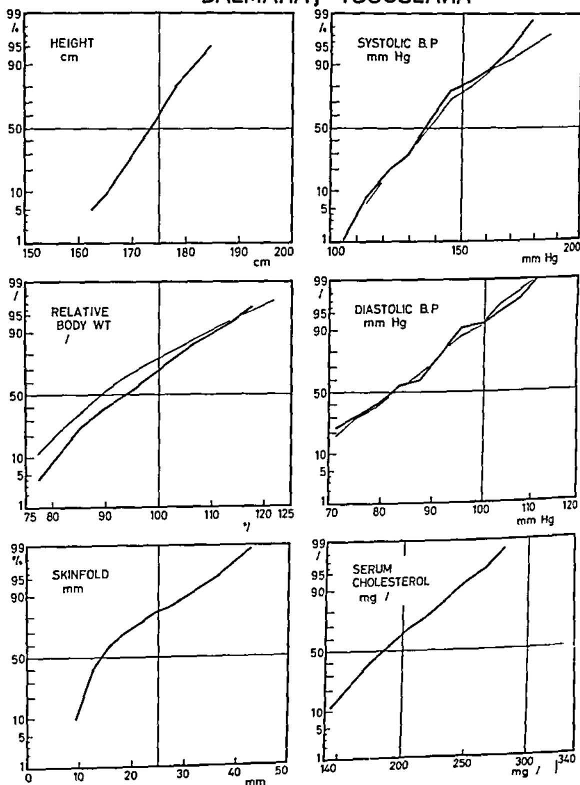

SLAVONIA, YUGOSLAVIA
HEIGHT cm
cm
SYSTOLIC B.P mm Hg
mm Hg
RELATIVE BODY WT
%
DIASTOLIC B.P mm Hg
mm Hg
SKINFOLD mm
mm
SERUM CHOLESTEROL mg
mg

Figure C3 2



DALMATIA, YUGOSLAVIA
HEIGHT
cm
SYSTOLIC B.P
mm Hg
RELATIVE
BODY WT
%
DIASTOLIC B.P
mm Hg
SKINFOLD
mm
SERUM
CHOLESTEROL
mg %

Figure C3 1

TABLE C3 4

Activity 1 vs Activity 2 Excess frequency of high values (deciles 8-10) of the variables observed among men of Activity 1, expressed as % of expectation from total numbers of men in Activities 1 plus 2 Also chi square values for the differences between observed and expected distributions

OCCUPATION	REL WT		Σ SKINFOLDS		SYST B P		DIAST B P		CHOLESTEROL	
	Excess	Chi²	Excess	Chi²	Excess	Chi²	Excess	Chi²	Excess	Chi²
Dalmatia										
1 94	79 7	16 02	57 9	15 20	18 6	0 54	30 4	1 72	12 0	0 18
1 13	11 1	1 30	11 8	6 14	16 5	0 90	16 5	0 90	-4 4	0
14 94	100 0	1 70	66 7	1 44	20 0	0	25 0	0 01	20 0	0
Slavonia										
1 94	19 5	7 44	18 8	7 28	-6 8	0 24	-6 3	0 26	-10 7	1 14
1 13	10 4	1 46	1 0	0	-1 5	0	-1 5	0	-2 4	0
14 94	21 4	1 20	17 6	0 70	34 8	1 69	-13 8	0 23	0 7	0

TABLE C3 5

Activity 2 vs Activity 3 Occupations 14 94 only Excess frequency as in Table C3 4 of high values among men of Activity 2

SAMPLE	REL WT		Σ SKINFOLDS		SYST B P		DIAST B P		CHOLESTEROL	
	Excess	Chi²	Excess	Chi²	Excess	Chi²	Excess	Chi²	Excess	Chi²
Dalmatia	23 1	1 66	48 1	6 06	24 4	1 52	15 0	0 49	19 4	0 91
Slavonia	54 8	6 17	55 8	6 35	15 4	0 46	33 3	2 65	54 8	7 08

TABLE C3 6

Occupation 1 13 vs 14 94 Excess frequency as in Table C3 4 of high values among men in Occupations 1 13 expressed as % of expectation from total numbers of men in Occupations 1 13 + 14 94

ACTIVITY	REL WT		Σ SKINFOLDS		SYST B P		DIAST B P		CHOLESTEROL	
	Excess	Chi²	Excess	Chi²	Excess	Chi²	Excess	Chi²	Excess	Chi²
Dalmatia										
1+2	70 4	13 29	38 1	6 82	12 0	0 12	13 8	0 26	16 3	0 46
1	5 0	0 14	3 3	0 05	10 1	0 27	2 6	0	0	0
2	60 0	0 61	14 3	0	35 5	0 20	40 0	0 05	37 9	0 22
Slavonia										
1+2	24 2	5 01	31 1	9 06	13 5	0 51	1 0	0	23 8	2 79
1	7 6	0 91	11 4	2 57	19 8	2 13	4 2	0 02	16 7	1 62
	0	0 19	25 0	0	4[illegible] 9	0	25 0	0	11 1	0

Probabilities p associated with chi square values 2 71 p = 0 10 3 84 p - 0 05 5 41 p 0 02 6 64 p 0 01 10 83 p - 0 001

subcutaneous fat is only about 2 to 3 mm

The Dalmatians are remarkable in regard to blood pressure in that they show no rise with age in either systole or diastole over most of the distribution the median values are actually lower at ages 55—59 than at 40—44 The ninth decile cutting points for systolic pressure in the Dalmatian men is 160 at ages 40—44 165 at ages 55—59 the corresponding values for diastolic pressure are 95 and 99 mm The Slavonians are little different in blood pressure except that they show more age trend the medians being lower than in Dalmatia at ages 40—44 but higher at ages 55—59

The serum cholesterol values are decidedly low according to findings in the United States and northern Europe and they are clearly lower in Dalmatia than in Slavonia, the medians for corresponding ages differing by about 12 mg cholesterol per 100 ml of serum

Physical Activity and Socio-Economic Status

In these population samples men with low physical activity tend to be more often relatively overweight obese and to have high blood pressure and relative hypercholesterolemia than their more active counterparts For example in the combined material for Dalmatia and Slavonia chance expectation would place equal numbers of men in Activity Classes 1 + 2 in the upper and in the lower 30 per cent categories of all men of equal age in the same area (deciles 8—10 and 1—3 respectively) But the data for men in these lower activity classes show 129 men in the upper 30 per cent group of relative weight and only 62 in the lower 30 per cent group Corresponding figures for Σ skinfolds are 138 and 48 men for systolic blood pressure 89 and 74 men for diastolic blood pressure 95 and 82 and for serum cholesterol 93 and 63 men

But attention to socio-economic status ignoring physical activity, shows even more striking departures from random chance Among the men in the upper socio-economic class (Occupations 1—13) 61 were in the decile classes 8—10 for relative weight and only 10 men in decile classes 1—3 Corresponding figures for Σ skinfolds are 67 and 13 men, for systolic blood pressure 36 and 26 for diastolic blood pressure 37 and 26 and for serum cholesterol 33 and 17 men

Obviously the interpretation of these data is complicated because of the high correlation (inverse) between physical activity and socio-economic status Almost no men of higher socio-economic status engage in physical activity (Class 3) in these populations relatively few men in the lower socio-economic class are sedentary Attempts at more detailed analysis are shown in Tables C3 4 C3 5 and C3 6 The general question of physical activity versus socio-economic status in regard to obesity high blood pressure etc is discussed in more detail in Section D below

Smoking Habits

Next to the sample in Velika Krsna also in Yugoslavia the men in Dalmatia and Slavonia tended to smoke less than the men in any of the other samples in these studies Table C3 7 shows the distribution of cigarette smoking habits by age It should be noted that pipe and cigar smoking is rare in these areas In both areas the percentage of men who had never smoked tends to fall with age while the percentage of stopped smokers has the opposite tendency so that the percentage of non-smokers is fairly constant at all ages In general the men of Dalmatia smoke

a little more than do the Slavonians Among those who do smoke the number of cigarettes smoked daily shows little age trend

Table C3.8 considers the association of smoking habits with other characteristics of these men In both areas the non smokers tend to be above the median for all men of their age in their sample in relative weight body fatness and blood pressure and these trends are statistically highly significant On the other hand the heavy smokers who regularly smoke 20 or more cigarettes daily show the opposite tendencies though only the Slavonian heavy smokers are significantly distinguished in this respect

In Dalmatia the serum cholesterol level shows little relationship to smoking habits but in Slavonia the non-smokers are unduly represented in the above median serum cholesterol class while the heavy smokers are significantly more apt to be below the median "Other" smokers in Slavonia who smoke regularly but fewer than 20 cigarettes a day tend to be below the cholesterol median

Electrocardiographic Findings

The electrocardiographic findings in rest and immediately after the standard exercise test are summarized in Tables C3 9 C3 10 C3 11 and C3 12 ECG abnormalities of any kind are remarkably uncommon in Dalmatia — in rest not a single case of definite old infarction (Code I 1) only 7 cases of S-T depression 3 of significant T wave inversion no A V blocks (partial or complete) only one left bundle branch block only 3 men (all 55—59) with auricular fibrillation or flutter 9 cases of sinus tachycardia in a total of 669 men aged 40—59 60 per cent of them over 50 years of age The exercise test added little more evidence of abnormality — 4 cases of ischemic S-T depression and 5 cases of arrhythmia where the records had shown none in rest

The Slavonian men showed more pathology but their records were still better than the usual expectation from other population samples There were 3 men with definite old myocardial infarction 10 of significant S-T depression and 12 of T wave inversion 2 left bundle branch blocks and 2 cases of atrial fibrillation or flutter However there were 79 cases of high amplitude R waves (left type) and 27 men with significant sinus tachycardia in rest The exercise test was more productive of ECG changes in Slavonia than in Dalmatia with three times as many cases of ischemic S-T depression where the records were normal in rest

Prevalence of Hypertension

Table C3 13 shows the prevalence of hypertension by age using two different criteria of diastolic blood pressure In general hypertension is more common in Slavonia than in Dalmatia especially among the oldest men (ages 55—59) Compared with all samples of men in these studies the Slavonians are in the middle of the distribution for hypertension whereas the Dalmatians are somewhat less prone to high blood pressure

Figures C3 3 and C3 4 show the distribution of the hypertensive men (diastolic pressure 95 mm or more) of Dalmatia and Slavonia in decile classes of relative body weight of the sum of the skinfolds and of serum cholesterol concentration In each case there is a striking curvilinear relationship hypertension being practically unrelated to these other variables except at the upper ends of their distributions For relative body weight and Σ skinfolds the men in the top 20 per cent of the

TABLE C3 7

Cigarette smoking habits of men of Dalmatia and Slavonia Percentage of men who never smoked, who had stopped who smoked 1-9, 10-19, 20 or more cigarettes daily at the time of their examination

SAMPLE	AGE	NEVER	QUIT	1-9	10-19	20 OR MORE
Dalmatia	40-44	39 4	7 1	7 1	30 9	15 5
"	45-49	33 3	8 9	7 2	27 8	22 8
"	50-54	26 3	11 0	8 1	32 1	22 5
"	55-59	26 9	16 8	6 3	23 7	26 3
"	40-59	30 0	11 6	7 2	28 4	22 8
Slavonia	40-44	31 3	10 8	9 8	26 5	21 6
"	45-49	30 4	13 8	8 8	31 0	16 0
"	50-54	20 2	13 1	10 1	35 9	20 7
"	55-59	26 5	14 0	8 8	32 6	18 1
"	40-59	26 4	13 2	9 3	32 3	18 8

a little more than do the Slavonians Among those who do smoke the number of cigarettes smoked daily shows little age trend

Table C3.8 considers the association of smoking habits with other characteristics of these men In both areas the non smokers tend to be above the median for all men of their age in their sample in relative weight body fatness and blood pressure and these trends are statistically highly significant On the other hand the heavy smokers who regularly smoke 20 or more cigarettes daily show the opposite tendencies though only the Slavonian heavy smokers are significantly distinguished in this respect

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TABLE C3 8

Smoking Number of men in Yugoslavia below (LOW) and above (HIGH) the age-specific medians, for age and area, of measured variables, classed according to smoking habits HEAVY = 20 or more, OTHER = 1-19 cigarettes daily

VARIABLE	*SAMPLE*	*NON-SMOKERS*		*HEAVY*		*OTHER*	
		LOW	HIGH	LOW	HIGH	LOW	HIGH
Relative Weight	Dalmatia	112	162	87	64	133	103
" "	Slavonia	78	198	87	44	181	106
Σ Skinfolds	Dalmatia	107	167	80	70	134	102
" "	Slavonia	82	194	87	44	177	110
Systolic B P	Dalmatia	122	153	79	72	129	106
" "	Slavonia	118	158	72	59	156	131
Diastolic B P	Dalmatia	122	154	84	67	125	116
" "	Slavonia	118	158	75	56	153	134
Serum Cholesterol	Dalmatia	137	137	82	68	111	121
" "	Slavonia	110	157	155	124	75	55

TABLE C3 9

DALMATIA, YUGOSLAVIA

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FI DING	ECG Code		AGE GROUP (Number of Men) 40 44 (84)	45 49 (184)	50 54 (211)	55 59 (190)
Total with reportable ECG Items	I IX		26 (309 5)	50 (271 7)	50 (237 0)	41 (215 8)
Q Waves	I	1	0	0	0	0
		2	1 (11 9)	2 (10 9)	3 (14 2)	2 (10 5)
		3	1 (11 9)	4 (21 7)	0	1 (5 3)
Axis Deviation	II					
Left		1	1 (11 9)	10 (54 3)	2 (9 5)	10 (52 6)
Rig t		2	0	1 (5 4)	0	0
High Amplitude R Waves	III					
Left type		1	3 (35 7)	6 (32 8)	8 (37 9)	2 (10 5)
Right type		2	0	2 (10 9)	1 (4 7)	0
S T Depression (rest)	IV					
S T J 1 mm or more horiz or downward s gment		1	0	0	0	1 (5 3)
S T J 0 5 1 mm horiz or downward segment		2	0	0	1 (4 7)	1 (5 3)
No S T J plus segment downward		3	1 (11 9)	1 (5 4)	1 (4 7)	1 (5 3)
S T J 1 mm or more upward segm nt		4	0	0	0	0
T Wave Negativity (rest)	V					
5 mm or more		1	0	0	0	0
1 mm to 5 mm		2	0	1 (5 4)	1 (4 7)	1 (5 3)
0 _ 1 mm		3	1 (11 9)	1 (5 4)	1 (4 7)	3 (15 8)
A V Conduction Defect	VI					
Com plete Block		1	0	0	0	0
Pa tial Block		2	0	0	0	0
P R over 0 21 second		3	0	0	0	0
Ac el rated Conduction		4	0	0	1 (4 7)	2 (10 5)
Ventricular Blocks	VII					
Left Bundle		1	0	0	0	1 (5 3)
Right Bundle		2	1 (11 9)	2 (10 9)	1 (4 7)	1 (5 3)
Incomplete Right Bundle		3	3 (35 7)	3 (16 3)	4 (19 0)	2 (10 5)
Intraventricular Block		4	0	0	1 (4 7)	0
A hythmias	VIII					
Premature Beats		1	2 (23 8)	0	0	4 (21 1)
V tricular tachyca dia		2	0	0	0	0
At ial fibrillation flutter		3	0	0	0	3 (15 8)
Supr vent tachycardia		4	0	0	0	0
Ventricul r rhythm		5	0	0	0	0
A V nodal rhythm		6	0	1 (5 4)	0	0
S nus tachycard a		7	1 (11 9)	3 (16 3)	4 (19 0)	1 (5 2)
Sinu bradycardia		8	0	1 (5 4)	0	0
Te n ally poor r cord	IX	8	0	0	0	0

TABLE C3 8

Smoking Number of men in Yugoslavia below (LOW) and above (HIGH) the age specific medians, for age and area, of measured variables, classed according to smoking habits HEAVY = 20 or more, OTHER = 1-19 cigarettes daily

VARIABLE	SAMPLE	NON-SMOKERS		HEAVY		OTHER	
		LOW	HIGH	LOW	HIGH	LOW	HIGH
Relative Weight	Dalmatia	112	162	87	64	133	103
" "	Slavonia	78	198	87	44	181	106
Σ Skinfolds	Dalmatia	107	167	80	70	134	102
" "	Slavonia	82	194	87	44	177	110
Systolic B P	Dalmatia	122	153	79	72	129	106
" "	Slavonia	118	158	72	59	156	131
Diastolic B P	Dalmatia	122	154	84	67	125	116
" "	Slavonia	118	158	75	56	153	134
Serum Cholesterol	Dalmatia	137	137	82	68	111	121
" "	Slavonia	110	157	155	124	75	55

TABLE C3 11

SLAVONIA YUGOSLAVIA

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDI^ G	ECG Code		AGE GROUP (Number of Men) 40 44 (102)	45-49 (180)	50-54 (196)	55 59 (216)
Total with reportable ECG Items	I IX		30 (294 1)	60 (333 3)	75 (382 7)	84 (388 9)
Q Waves	I	1	0	2 (11 1)	1 (5 1)	0
		2	0	2 (11 1)	1 (5 1)	3 (13 9)
		3	0	2 (11 1)	1 (5 1)	1 (4 6)
Axis Deviation	II					
Left		1	3 (29 4)	8 (44 4)	9 (45 9)	20 (92 6)
Right		2	0	0	0	0
High Amplitude R Waves	III					
Left type		1	14 (137 3)	15 (83 3)	23 (117 3)	27 (125 0)
Right type		2	0	0	1 (5 1)	0
S T Depression (rest)	IV					
5 T J 1 mm or more horiz or downward segment		1	0	0	0	1 (4 6)
S T J 0 5 1 mm horiz or downward segment		2	0	2 (11 1)	2 (10 2)	2 (9 3)
No S T J plus segment downward		3	0	2 (11 1)	0	1 (4 6)
S T J 1 mm or more upward segment		4	0	1 (5 6)	0	1 (4 6)
T Wav Negativity (rest)	V					
5 mm or more		1	0	0	1 (5 1)	0
1 mm to 5 mm		2	0	3 (16 7)	3 (15 3)	5 (23 1)
0 _ 1 mm		3	1 (9 8)	8 (44 4)	7 (35 7)	10 (46 3)
A V Conduction Defect	VI					
Complete Block		1	0	0	0	0
P rtial Block		2	0	0	0	0
P R o e 0 21 s cond		3	0	1 (5 6)	0	0
A elerated Conduction		4	0	0	1 (5 1)	1 (4 6)
V ntricular Blocks	VII					
Left B indle		1	0	0	1 (5 1)	1 (4 6)
Right Bundl		2	0	1 (5 6)	0	2 (9 3)
Incomplet R ght Bundl		3	0	3 (16 7)	0	1 (4 6)
Intraventr cular Block		4	0	0	0	1 (4 6)
A hythmia	VIII					
P matu B ats		1	0	0	0	5 (23 1)
V nt ul tachyca dia		2	0	0	0	0
Atr l f b illation flutter		3	0	0	1 (5 1)	1 (4 6)
S p a vent tachy a dia		4	0	0	0	1 (4 6)
\ tricular rhythm		5	0	0	0	0
A V nodal hythm		6	0	0	0	0
S nu tachyc rdia		7	3 (29 4)	9 (50 0)	8 (40 8)	7 (32 4)
S br dy a d a		8	0	0	0	0
T hn lly poo r co d	IX	8	0	0	1 (5 1)	0

TABLE C3 10

DALMATIA YUGOSLAVIA

FREQUENCY OF POST-EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1,000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (83)	45-49 (179)	50 54 (209)	55 59 (187)
Exercise tests not made or incomplete	X 1 X 2	1 (12 0)	5 (27 9)	2 (9 6)	3 (16 0)
S-T Depression post exercise (none at rest)	XI				
S-T - J 1 mm or more, horiz or downward segment	1	0	0	0	1 (5 3)
S-T - J 0 5 - 1 mm , horiz or downward segment	2	0	1 (5 6)	1 (4 8)	0
No S-T-J plus segment downward	3	0	1 (5 6)	0	0
S-T - J 1 mm or more upward segment	4	0	2 (11 2)	1 (4 8)	1 (5 3)
T Wave Negativity post-exercise (none at rest)	XII				
-5 mm or more	1	0	0	0	0
-1 to -5 mm	2	0	0	0	0
0 ± 1 mm	3	0	0	2 (9 6)	2 (10 7)
Arrhythmias post-exercise (none at rest)	XV 1	0	1 (5 6)	1 (4 8)	3 (16 0)
Technically poor post exercise records	XI 8	0	1 (5 6)	0	1 (5 3)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

At Rest					
Large Q Waves	I 1	0	0	0	0
Lesser Q Waves with Negative T Waves	I 2, 3 + V 1 2	0	1 (5 5)	0	0
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	1 (11 8)	1	2 (9 5)	1 (5 3)
S-T Depression as sole anomaly	IV 1-4 only	1 (11 8)	1 (5 5)	2 (9 5)	1 (5 3)
High Amplitude R with S-T Depression	III 1 + IV 1-4	0	1 (5 5)	0	0
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2 4	1 (11 8)	2 (10 9)	2 (9 5)	2 (10 5)
Arrhythmias	VIII 2 6	0	1 (5 5)	0	3 (15 8)
Post exercise					
S-T Depression as sole anomaly	XI 1-4 only	0	1 (5 6)	2 (9 6)	2 (10 7)
Negative T as sole anomaly	XII 1-3 only	0	0	1 (4 8)	1 (5 3)
Ventricular Conduction Defect as sole anomaly	XIV 1 2 4 only	0	0	0	0
Arrhythmias as sole anomaly	XV 1 only	0	1 (5 6)	1 (4 8)	2 (10 7)

TABLE C3 11

SLAVONIA YUGOSLAVIA

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code		AGE GROUP (Number of Men) 40 44 (102)	45 49 (180)	50 54 (196)	55 59 (216)
Total with reportable ECG Items	I IX		30 (294 1)	60 (333 3)	75 (382 7)	84 (388 9)
Q Waves	I	1	0	2 (11 1)	1 (5 1)	0
		2	0	2 (11 1)	1 (5 1)	3 (13 9)
		3	0	2 (11 1)	1 (5 1)	1 (4 6)
Axis Deviation	II					
Left		1	3 (29 4)	8 (44 4)	9 (45 9)	20 (92 6)
Right		2	0	0	0	0
High Amplitude R Waves	III					
Left type		1	14 (137 3)	15 (83 3)	23 (117 3)	27 (125 0)
Right type		2	0	0	1 (5 1)	0
S T Depression (rest)	IV					
S T J 1 mm or more horiz or downward segment		1	0	0	0	1 (4 6)
S T J 0 5 1 mm horiz or downward segment		2	0	2 (11 1)	2 (10 2)	2 (9 3)
No S T J plus segment downward		3	0	2 (11 1)	0	1 (4 6)
S T J 1 mm or more upward segment		4	0	1 (5 6)	0	1 (4 6)
T Wave Negativity (rest)	V					
5 mm or more		1	0	0	1 (5 1)	0
1 mm to 5 mm		2	0	3 (16 7)	3 (15 3)	5 (23 1)
0 _ 1 mm		3	1 (9 8)	8 (44 4)	7 (35 7)	10 (46 3)
A V Conduction Defect	VI					
Complete Block		1	0	0	0	0
Partial Block		2	0	0	0	0
P R over 0 21 second		3	0	1 (5 6)	0	0
Accelerated Conduction		4	0	0	1 (5 1)	1 (4 6)
Ventricular Blocks	VII					
Left Bundle		1	0	0	1 (5 1)	1 (4 6)
Right Bundle		2	0	1 (5 6)	0	2 (9 3)
Incomplete Right Bundle		3	0	3 (16 7)	0	1 (4 6)
Intraventricular Block		4	0	0	0	1 (4 6)
Arrhythmias	VIII					
Premature Beat		1	0	0	0	5 (23 1)
Ventricular tachycardia		2	0	0	0	0
Atrial fibrillation flutter		3	0	0	1 (5 1)	1 (4 6)
Supraventricular tachycardia		4	0	0	0	1 (4 6)
Idioventricular rhythm		5	0	0	0	0
A V nodal rhythm		6	0	0	0	0
Sinus tachycardia		7	3 (29 4)	9 (50 0)	8 (40 8)	7 (32 4)
Sinus bradycardia		8	0	0	0	0
Technically poor records	IX	8	0	0	1 (5 1)	0

TABLE C3 12

SLAVONIA YUGOSLAVIA

FREQUENCY OF POST-EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1,000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40 44 (101)	45-49 (175)	50 54 (189)	55 59 (204)
Exercise tests not made or incomplete	X 1 X 2	1 (9 8)	5 (27 8)	7 (35 7)	12 (55 6)
S T Depression post exercise (none at rest)	XI				
S-T - J 1 mm or more horiz or downward segment	1	0	3 (17 1)	1 (5 3)	1 (4 9)
S-T - J 0 5 - 1 mm horiz or downward segment	2	0	2 (11 4)	2 (10 6)	3 (14 7)
No S T-J plus segment downward	3	0	0	0	0
S-T J 1 mm or more upward segment	4	1 (9 9)	1 (5 7)	0	2 (9 8)
T Wave Negativity post-exercise (none at rest)	XII				
-5 mm or more	1	0	0	0	0
-1 to 5 mm	2	0	0	0	2 (9 8)
0 ± 1 mm	3	0	3 (17 1)	1 (5 3)	0
Arrhythmias post exercise (none at rest)	XV 1	0	0	1 (5 3)	4 (19 6)
Technically poor post exercise records	XI 8	1 (9 9)	0	2 (10 6)	1 (4 9)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

At Rest					
Large Q Waves	I 1	0	2 (11 1)	1 (5 1)	0
Lesser Q Waves with Negative T Waves	I 2 3 + V 1 2	0	0	0	0
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	0	3 (16 7)	2 (10 2)	4 (18 5)
S-T Depression as sole anomaly	IV 1-4 only	0	2 (11 1)	0	0
High Amplitude R with S-T Depression	III 1 + IV 1-4	0	2 (11 1)	2 (10 2)	1 (4 6)
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1, 2 4	0	1 (5 6)	1 (5 1)	4 (18 5)
Arrhythmias	VIII 2 6	0	0	1 (5 1)	2 (9 3)
Post-exercise					
S T Depression as sole anomaly	XI 1 4 only	0	3 (17 1)	0	4 (19 6)
Negative T as sole anomaly	XII 1-3 only	0	3 (17 1)	1 (5 3)	1 (4 9)
Ventricular Conduction Defect as sole anomaly	XIV 1 2 4 only	0	0	0	0
Arrhythmias as sole anomaly	XV 1 only	0	0	1 (5 3)	1 (4 9)

TABLE C3 13

Prevalence of diastolic hypertension (95 or more 100 or more mm Hg fifth phase) among men classed by age Percentage of men in Dalmatia and Slavonia who are hypertensive compared with the average for all 18 samples of men

SAMPLE	40 44		45-49		50-54		55-59	
	95mm	100mm	95mm	100mm	95mm	100mm	95mm	100mm
Dalmatia	13 2	7 2	14 8	8 7	18 0	7 6	16 1	9 3
Slavonia	13 7	8 8	17 1	11 0	11 2	8 1	22 1	12 4
Mean 18 samples	13 6	7 9	15 6	8 9	20 9	13 5	21 5	13 8

TABLE C3 12

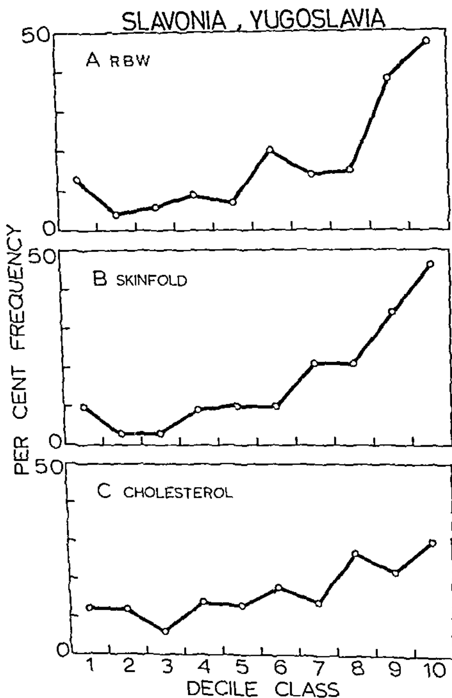
SLAVONIA YUGOSLAVIA

FREQUENCY OF POST-EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (101)	45-49 (175)	50 54 (189)	55 59 (204)
Exercise tests not made or	X 1				
incomplete	X 2	1 (9 8)	5 (27 8)	7 (35 7)	12 (55 6)
S-T Depression post-exercise					
(none at rest)	XI				
S T - J 1 mm or more horiz					
or downward segment	1	0	3 (17 1)	1 (5 3)	1 (4 9)
S T - J 0 5 - 1 mm , horiz or					
downward segment	2	0	2 (11 4)	2 (10 6)	3 (14 7)
No S-T-J plus segment downward	3	0	0	0	0
S T - J 1 mm or more upward					
segment	4	1 (9 9)	1 (5 7)	0	2 (9 8)
T Wave Negativity post exercise					
(none at rest)	XII				
-5 mm or more	1	0	0	0	0
-1 to -5 mm	2	0	0	0	2 (9 8)
0 + 1 mm	3	0	3 (17 1)	1 (5 3)	0
Arrhythmias post-exercise	XV				
(none at rest)	1	0	0	1 (5 3)	4 (19 6)
Technically poor post-exercise					
records	XI 8	1 (9 9)	0	2 (10 6)	1 (4 9)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

ECG FINDING	ECG Code	40-44	45-49	50 54	55 59
At Rest					
Large Q Waves	I 1	0	2 (11 1)	1 (5 1)	0
Lesser Q Waves	I 2 3 +				
with Negative T Waves	V 1, 2	0	0	0	0
Deeply Negative T as sole	V 1				
anomaly	only	0	0	0	0
Other Negative T as sole	V 2 3				
anomaly	only	0	3 (16 7)	2 (10 2)	4 (18 5)
S T Depression as sole	IV 1-4				
anomaly	only	0	2 (11 1)	0	0
High Amplitude R	III 1 +				
with S-T Depression	IV 1-4	0	2 (11 1)	2 (10 2)	1 (4 6)
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2 4	0	1 (5 6)	1 (5 1)	4 (18 5)
Arrhythmias	VIII 2 6	0	0	1 (5 1)	2 (9 3)
Post-exercise					
S-T Depression as sole	XI 1-4				
anomaly	only	0	3 (17 1)	0	4 (19 6)
Negative T as sole	XII 1-3				
anomaly	only	0	3 (1 1)	1 (5 3)	1 (4 9)
Ventricular Conduction Defect as	XIV 1 2 4				
sole anomaly	only	0	0	0	0
Arrhythmias	XV 1				
as sole anomaly	only	0	0	1 (5 3)	1 (4 9)



SLAVONIA , YUGOSLAVIA
50
A RBW
0
50
B SKINFOLD
0
50
C CHOLESTEROL
0
PER CENT FREQUENCY
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

Figure C3 4

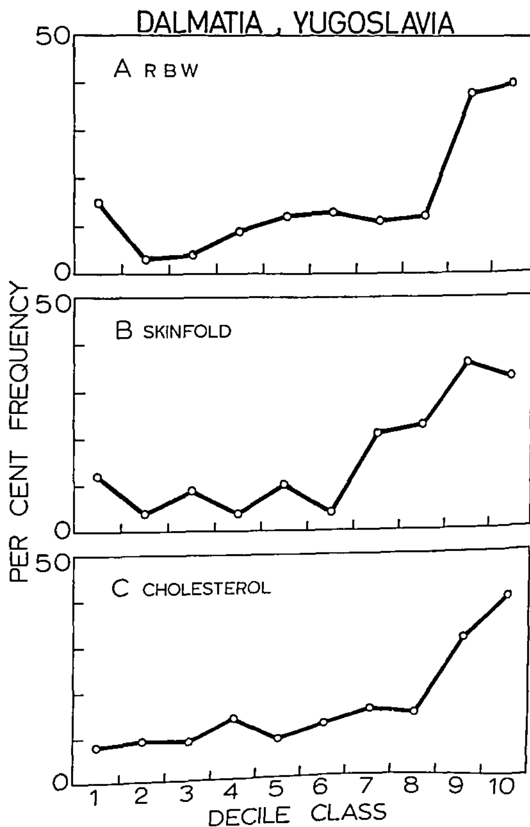

DALMATIA , YUGOSLAVIA
A RBW
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
50
0
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

Figure C3 3

TABLE C3 14

Prevalence of overweight (110 or more and 120 or more per cent of 'standard" average for height and age) Percentage of men in Dalmatia and Slavonia classed by age who are overweight compared with the average for all 18 samples of men

SAMPLE	40-44		45 49		50 54		55-59	
	110%	120%	110%	120%	110%	120%	110%	120%
Dalmatia	9 4	2 4	10 4	2 2	8 1	2 8	11 6	4 2
Slavonia	14 7	6 9	19 2	10 4	12 7	6 1	11 6	3 7
Mean 18 samples	20 9	8 4	19 4	6 9	18 1	6 7	16 8	7 3

distributions are far more apt to be hypertensive than the men in the remainder of the distributions For serum cholesterol the situation is similar though not quite so dramatic in Slavonia

The general picture, then is that the prevalence of hypertension is unrelated to body weight at all values below relative weight of about 110 per cent to Σ skinfolds at all values below about 20 mm and to serum cholesterol below about 240 mg per 100 ml

Prevalence of Overweight

The prevalence of overweight, defined as relative body weight of 110 per cent and 120 per cent of the standard values for given height and age in the Appendix is summarized in Table C3 14 Overweight is not common in Dalmatia and is only moderately frequent in Slavonia With 110 per cent of the standard as the criterion 10 per cent of the Dalmatians and 14 per cent of the Slavonians are overweight the corresponding figures for U S railroad switchmen and for men in Crevalcore Italy, are 37 and 34 per cent, respectively

Figures C3 5 and C3 6 show the distribution of the overweight (110 per cent of standard) men in decile classes of serum cholesterol diastolic and systolic blood pressure The prevalence of overweight increases with increasing values of these other variables The relationship is very marked and curvilinear with blood pressure less striking but still highly significant with serum cholesterol For example men with systolic blood pressure less than 130 mm are rarely overweight more than 20 per cent of men with systolic pressure of the order of 160 or more are overweight Men with serum cholesterol values of 180 mg per 100 ml or less are seldom overweight at cholesterol values of the order of 250 about a fourth of the men are overweight

Summary

Data are presented on 1476 men aged 40—59, comprising 94 8 per cent of all men of those ages in two rural areas of Dalmatia and Slavonia Yugoslavia In both areas most of the men were small-scale farmers Only 12 6 per cent of these men were sedentary or engaged in light physical activity, 76 7 per cent of them habitually did heavy physical work

The men in Dalmatia averaged about 5 cm taller than the men in Slavonia in both areas height tended to decrease slightly with age In body fatness the men in both areas were similarly thin The two areas were similar in the distribution of blood pressure but hypertension was somewhat less common in Dalmatia than in Slavonia In Dalmatia there was almost no age trend in blood pressure over the range 40 through 50 years Serum cholesterol concentration was relatively low in both areas but more so in Dalmatia

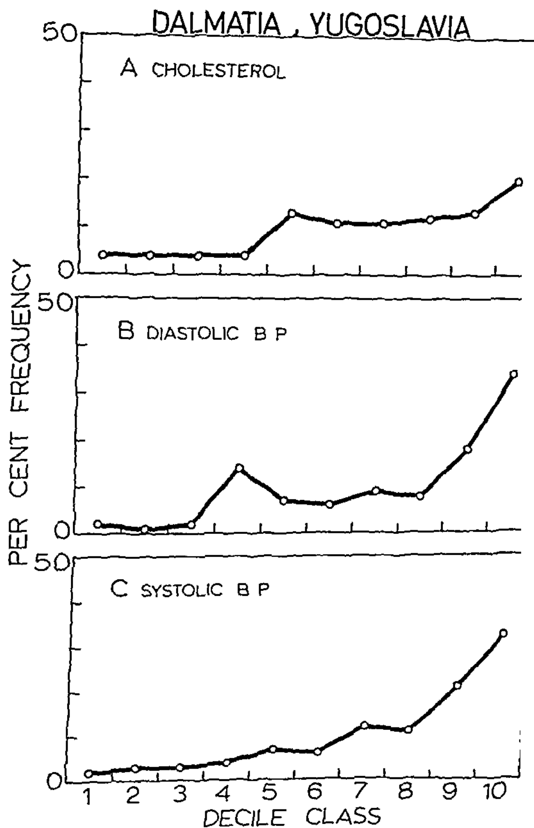
Relatively high body weight obesity high blood pressure and high serum cholesterol were more common among the less active men in the upper socio-economic class than among the more active men in the lower class

About 40 per cent of the men in both areas were non-smokers and only about 20 per cent of them smoked 20 or more cigarettes daily Compared with the smokers the non-smokers tended to be more often overweight obese and to have high blood pressure High serum cholesterol values tended to be less common among the men who smoked

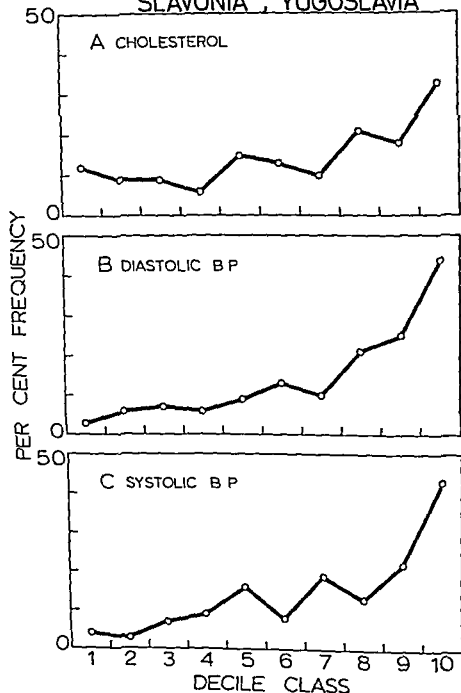
TABLE C3 14

Prevalence of overweight (110 or more and 120 or more per cent of "standard" average for height and age) Percentage of men in Dalmatia and Slavonia classed by age who are overweight compared with the average for all 18 samples of men

SAMPLE	40 44		45-49		50 54		55-59	
	110%	120%	110%	120%	110%	120%	110%	120%
Dalmatia	9 4	2 4	10 4	2 2	8 1	2 8	11 6	4 2
Slavonia	14 7	6 9	19 2	10 4	12 7	6 1	11 6	3 7
Mean 18 samples	20 9	8 4	19 4	6 9	18 1	6 7	16 8	7 3



DALMATIA, YUGOSLAVIA
A CHOLESTEROL
B DIASTOLIC B P
C SYSTOLIC B P
PER CENT FREQUENCY
50
0
50
0
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS



prevalence of OVERWEIGHT vs A-cholesterol, B-diastolic, C-systolic blood pressure

Figure C3 6

20 or more cigarettes daily than among the other smokers or the non-smokers

Significant electrocardiographic abnormalities in rest or after standard exercise were rare in Dalmatia and not frequent in Slavonia

The prevalence of hypertension showed a marked curvilinear relationship to relative body weight body fatness and serum cholesterol resulting in no association except at the upper ends of the distributions of those variables

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Local help was provided in Dalmatia by Dr Dušan Jurela Mr Ph Marcel Barbieri and Zlata Srzic and in Slavonia by Dr A Vugrincic Important counsel and aid was given by Dr Ivo Brodarec and Dr Edvin Ferber

C4 MEN IN RURAL EAST AND WEST FINLAND

by Martti J Karvonen (Helsinki) Gunnar Blomqvist (Stockholm) Veikko Kallio (Turku) Esko Orma (Helsinki) Sven Punsar (Helsinki) Pentti Rautaharju (Halifax) Juha Takkunen (Helsinki) and Ancel Keys (Minneapolis)

Introduction

Finland is of great interest in regard to the epidemiology of coronary heart disease because of the reported very high incidence and mortality of the disease especially in East Finland (Karelia) Interest is enhanced by the fact that Finland is a country where relatively few people are obese or sedentary the majority of the population live quietly in the rural countryside and medical standards are high

The mortality rate ascribed to coronary heart disease in Finland has long been the highest in Europe and the most recent data indicate that among men aged 40—59 the Finns now have the highest death rate in the world from this cause 372 4 deaths per 100 000 in 1961 the comparable figure for the United States in 1961 is 365 2 This is not surprising in 1956 and 1959 our personal surveys of patients in several parts of Finland as well as in Helsinki everywhere gave the same picture of extraordinary prevalence of the disease verified by electrocardiographic and other evidence of myocardial infarction The coronary patients generally occupied over 30 per cent of all medical beds for adult patients in the general hospitals

In 1956 medical and dietary surveys were made of substantially all reportedly healthy middle-aged men in two series of villages in the area of Finnish Karelia (East Finland) centered on the town of Joensuu Some of the data have been reported (Roine *et al* 1958 Keys *et al* 1958b Karvonen *et al* 1959) The very high intake of butterfat is noteworthy

In 1959 the same general areas with some changes in the geographical limits were covered in the systematic studies reported in part here But in 1959 the attempt was made to examine *all* men then aged 40—59 who were permanent residents of the selected areas The final rosters of eligible men prepared from the excellent official *registries* were checked and the result was 823 men in East Finland and 887 in West Finland who were invited for the examinations 99 3 and 97 0 per cent of those men respectively were examined in detail in September October 1959

Methods and criteria were the same as used with the samples of men in other countries reported here and comparability was assured by adding experienced professional personnel from the U S A Yugoslavia and Sweden to the Finnish team

East Finland (Karelia)

Karelia is the land of the epic Kalevala of Finland and in spite of the proximity to Russia the population is entirely Finnish with no trace of any Slav element There is an appreciable number of adherents to the Greek Orthodox faith but these people too are purely Finnish in race language and outlook After the last war with the U S S R a large area of the most prosperous part of Karelia was taken over by the U S S R and the Finnish population there as a body elected to move across the new border so as to remain in Finland Most of these refugees were settled in other parts of Finland remote from Karelia and the study population is mainly made up of men from families that have not moved for generations

The headquarters of the study area is the small village of Ilomantsi very close to the Russian border and about 90 kilometers from the town of Joensuu in which there is a large modern hospital an airport and railroad The population is sparse and a relatively large geographical area was included in order to provide the requisite number of subjects In general the population lives on small farms or clearings in the forest and the men work at logging for the paper pulp industry during the long winters The economic level is low compared to the rest of Finland but the population tends to remain stable in this sub-arctic land At the time of the study communication with the rest of Finland was by rather poor road to Joensuu currently a railroad is under construction to Ilomantsi

The age distributions of the population studied in 1959 reflected some differential loss of the younger men in the two wars with the U S S R There were fewer men aged 40—44 than in the age group 45—49 (207 vs 238 men)

West Finland

A series of small villages and individual farms in the southwest of Finland not far inland from the city of Turku comprises the West Finland area There is no other industry besides agriculture in the actual area of study but the nearby port city of Turku is industrial and maritime as well as being a commercial center and the seat of a university and medical school The dominant Finnish element of the population is hardly diluted by the long rule of Sweden Some of the population dispossessed as a result of World War II from what is now Soviet Karelia were settled in this West Finland area in the late 1940's but these people are now well integrated and in general the population is stable

The climate is sub-arctic but somewhat less severe than that of Karelia and the farms are more productive especially of small grains and potatoes As in East Finland dairying is prominent and much butter milk and cheese is locally consumed though perhaps the per-capita consumption is less than in Karelia

The age structure of the populations of men examined in *1959 reflects the* heavy losses of younger men in the two wars against U S S R Successive 5-year age groups from 40—59 years provided 19 6 26 0 28 6 and 25 8 per cent of the total

Distribution by Physical Activity and Occupation

Table C4 1 gives the distribution by age of the Finnish men classed according *to physical activity* For all ages combined 71 1 per cent of the East Finns and 77 2 per cent of the men in the West were in the heavy (Grade 3) Activity Class The high intensity of

TABLE C4 1

Physical activity men in East and in West Finland classed by age and habitual physical activity (ACT ," 1 = sedentary and light 2 = moderate 3 = heavy work) N = total men Table entries are percentages of all men of given age in the area

AGE	E FINLAND N = 816			W FINLAND N = 860		
	ACT 1	ACT 2	ACT 3	ACT 1	ACT 2	ACT 3
40-44	9 1	22 0	68 9	8 9	14 8	76 3
45-49	11 3	15 1	73 6	7 1	12 9	79 9
50-54	11 2	14 2	74 6	11 4	14 3	74 3
55-59	14 6	19 3	66 1	8 1	13 5	78 4
40-59	11 4	17 5	71 1	9 0	13 8	77 2

physical work that characterized many of these men led to an original classification in four grades Grade 4 being "extreme" but this latter group was combined with those in Grade 3 because of difficulty in deciding where some men belonged and because in none of the other 16 samples studied in other countries was there a sizeable number of men who could be put in Grade 4 with security

Over all ages 40—59 only 11 4 per cent of men in the East and 9 0 per cent in the West could be classed as being sedentary or doing only light work In East Finland but not in the West the percentage of men in Activity Class 1 rose with age but the trend is not marked In neither area was there any tendency for the percentage of Activity Class 3 men to change with age In general there are no significant differences between the two areas in regard to physical activity

Table C4 2 summarizes the distributions in regard to general type of occupation In East Finland there were a few more men in the business professional and officials categories but in both areas these men are a very small minority In both areas almost 70 per cent of the men are small-scale farmers and woodsmen usually devoting the winters to logging and working on their own farms during the rest of the year

Distributions of Six Measured *Variables*

Table C4 3 gives the median values and those medians expressed as percentage of the averages of the medians for all men in these cooperative studies for height relative body weight body fatness (Σ skinfolds) systolic and diastolic (5th phase) blood pressure and serum cholesterol concentration Details of the distributions of these variables are given in the Appendix Figures C4 1 and C4 2 show the cumulative frequency distributions of these variables Because height Σ skinfolds and serum cholesterol show little or no age trend over the range 40—59 years in this material all ages 40—59 are combined in the graphs on these variables For relative body weight systolic and diastolic blood pressure the heavy line is for ages 40—49 the light line for ages 50—59

In both areas of Finland height and serum cholesterol show substantially normal distributions as does diastolic blood pressure in East Finland (Karelia) but not in the west The relative body weight distributions are not far from normal in both areas Σ skinfolds are grossly non-normal in distribution in Finland as in other areas

The men in West Finland consistently tend to be taller relatively heavier fatter (but still very lean) than their agecounterparts in the East On the other hand the East Finns tend to have higher blood pressure and higher serum cholesterol values Except for Σ skinfolds these differences are all so obviously significant that detailed probability estimates are unnecessary

When these Finns are compared with the average of all 18 samples the men in the East are slightly below and those in the West slightly above average height In relative weight the East Finns are significantly underweight while the men in the West tend if anything to be a little heavier for their height and age than the general average Both groups but especially the East Finns are much thinner than the average of all men

In blood pressure the East Finns clearly tend to have higher pressures both in systole and in diastole than the general average of the 18 samples The West Finns tend to slightly higher systolic and lower diastolic blood pressures than the general average

TABLE C4 2

Occupation of men in East and in West Finland classed Codes 1-15 (business, professional business owners and government officials) Codes 66-69 71-75 (farming agriculture and forestry) and all others Table entries are percentages of all men in the area

OCCUPATION	E FINLAND	W FINLAND
Codes 1-15	8 3	4 6
66-69 71-75	68 7	69 5
All Other	23 0	25 9

TABLE C4 3

Medians for men classed by age in East and in West Finland and these values expressed as percentages of the averages of the medians for all 18 samples of men

AREA	VARIABLE	MEDIAN VALUES				MEDIAN % OF AVERAGE			
		40-44	45-49	50-54	55-59	40-44	45-49	50-54	55-59
E FINLAND	Height (cm.)	168	168	168	167	98 9	99 3	99 8	99 6
	Rel Wt (")	94	94	93	90	95 8	97 7	97 7	95 6
'	Σ Skinfolds	13	15	14	14	61 3	73 5	67 6	70 4
'	Syst B P	141	140	149	153	107 6	105 3	108 8	108 8
'	Diast B P	87	88	90	90	107 4	108 1	107 9	106 8
'	Serum Chol	265	272	262	259	128 4	131 2	125 4	125 4
W FINLAND	Height (cm)	173	171	172	170	101 9	101 1	102 2	101 4
	Rel Wt (%)	98	96	97	95	99 9	99 8	101 9	101 0
	Σ Skinfolds	16	16	16	16	75 5	78 4	77 3	80 4
	Syst B P	133	135	139	143	101 5	101 5	101 5	101 7
	Diast B P	80	80	82	82	98 8	98 3	98 3	97 3
	Serum Chol	248	255	257	251	120 2	123 0	123 0	121 5

physical work that characterized many of these men led to an *original classification in four grades* Grade 4 being "extreme" but this latter group was combined with *those in* Grade 3 because of difficulty in deciding where *some* men belonged and because in none of the *other 16 samples* studied in other countries was there a *sizeable* number of men who *could be put in Grade 4* with security

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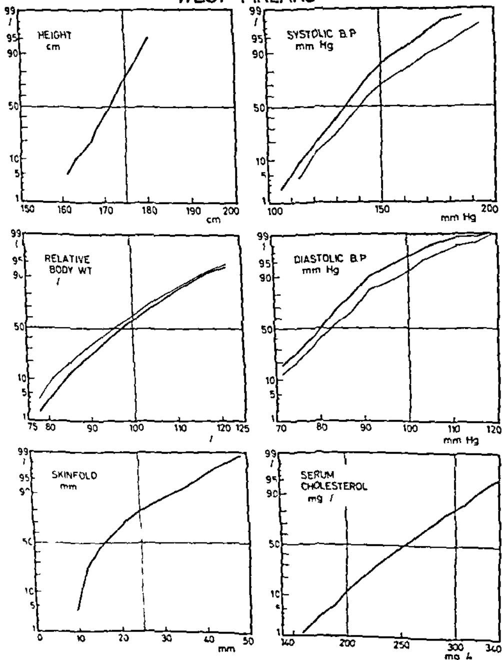

WEST FINLAND
HEIGHT
cm
SYSTOLIC B.P
mm Hg
RELATIVE
BODY WT
%
DIASTOLIC B.P
mm Hg
SKINFOLD
mm
SERUM
CHOLESTEROL
mg %
cm
mm Hg
%
mm Hg
mm
mg %

Figure C4 2

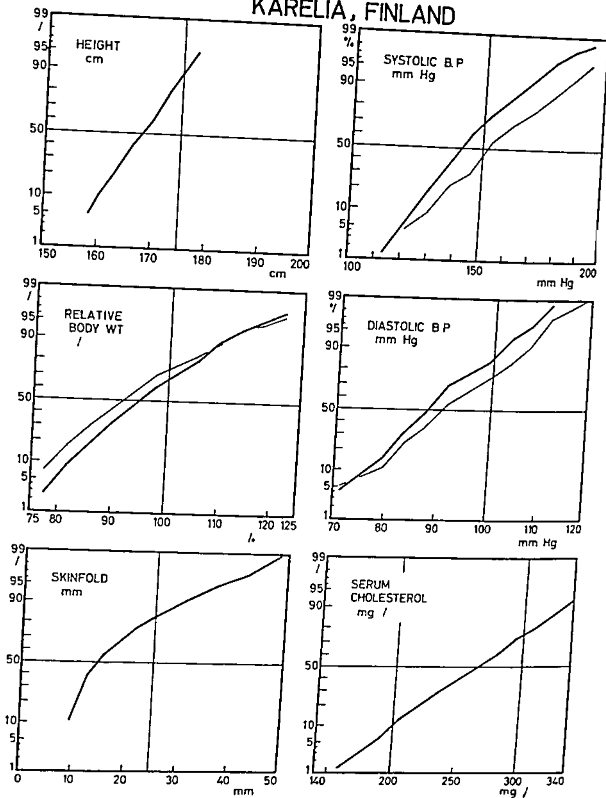
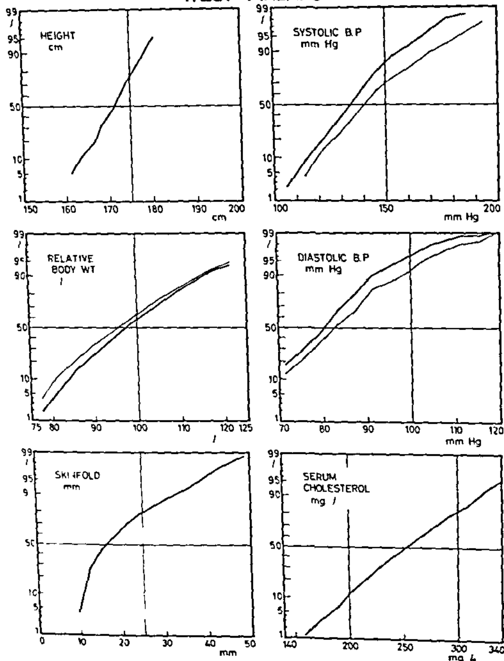

KARELIA, FINLAND
HEIGHT
cm
cm
SYSTOLIC B.P.
mm Hg
mm Hg
RELATIVE
BODY WT
%
%
DIASTOLIC B.P.
mm Hg
mm Hg
SKINFOLD
mm
mm
SERUM
CHOLESTEROL
mg %
mg %

Figure C4 1



WEST FINLAND
HEIGHT cm
SYSTOLIC B.P mm Hg
RELATIVE BODY WT
DIASTOLIC B.P mm Hg
SKINFOLD mm
SERUM CHOLESTEROL

Figure C4 2

Physical Activity and Socio-Economic Status

In both East and West Finland the relative frequency of overweight and of obesity decreases as physical activity increases With decile classes 8—10 of relative body weight representing overweight chance distribution would result in an expectation of about 24 43 and 155 "overweight" men in Eeast Finland in Activity Classes 1 2 and 3 respectively the observed numbers are 36 55 and 131 men respectively The corresponding numbers for "overfat" (deciles 8—10 in Σ skinfolds) in East Finland are 26, 44 and 161 men in Activity Classes 1, 2 and 3 the observed numbers are 45, 58 and 128 men, respectively Similar relationships were found in West Finland Frequency of relatively high blood pressure or serum cholesterol values was not significantly related to physical activity in either area

When physical activity is ignored and comparison is made between men in the upper socio-economic class (Occupations 1—13) with those in the lower class (Occupations 14—92 94) similar significant differences are found in the frequency of overweight and of obesity the men in the upper socio-economic class being more often overweight and fat

Obviously, the analysis is complicated by the high correlation (inverse) between physical activity and socio-economic status Tables C4 4 C4 5 and C4 6 summarize some findings when both physical activity and occupation are considered simultaneously

Within broad socio-economic classes there are no significant differences in the distributions of overweight or obese men between Activity Classes 1 and 2 but there are highly significant differences between Activity Classes 2 and 3 within the lower socio-economic class of men (Table C4 5) Higher diastolic blood pressures are also overly represented in Activity Class 2 as compared with Activity Class 3 in West but not in East Finland

Comparisons between upper and lower socio-economic classes in regard to the frequency of high values of these variables are made in Table C4 6 In general overweight and obesity are overly represented in the upper socio economic class even when physical activity is relatively constant

Smoking Habits

Smoking has long been common in Finland except during the years 1939—45 when war severely restricted the importation of tobacco At the time of the examinations reported here (1959) 68 5 per cent of the East and 57 2 per cent of the West Finns studied were cigarette smokers Among these rural men there are also a few pipe smokers cigars are occasionally smoked on festive occasions

In East Finland an appreciable number of the smokers use the "Russian type" of cigarette with a hollow paper mouthpiece and containing only a relatively small amount of tobacco this type is rarely used in West Finland in recent years and this difference should be noted in comparing the intensity of smoking in the two areas

In East Finland 31 4 per cent of all the men smoked 20 or more cigarettes daily and so could be considered to be "heavy' smokers in our classification in West Finland only 14 8 per cent of the men are in this category Though these values are not completely comparable because of the difference in cigarette types it seems clear that the men in Karelia more often tend to smoke and to smoke heavily than the men in the study area of West Finland

The associations of differences in smoking habits with differences in other characteristics are examined in Table

TABLE C4 4

Activity 1 vs Activity 2 Excess frequency o high values (deciles 8 10) of the variables observed among men of Activity 1 expressed as % of expectation from total numbers of men in Activities 1 plus 2 Also chi-square values for the differences between observed and expected distributions

OCCUPATION	REL WT Excess	Chi²	Σ SKINFOLDS Excess	Chi²	SYST B P Excess	Chi²	DIAST B P Excess	Chi²	CHOLESTEROL Excess	Chi²
East Finland										
1 94	9 8	0 68	17 5	3 47	10 5	0 23	11 1	0 41	-6 4	0 10
1-13	9 1	0 43	7 9	0 62	17 6	0 19	-4 3	0	1 1	0
14 94	19 5	1 04	12 4	0 39	14 3	0 19	28 0	1 53	0 8	0
West Finland										
1 94	16 9	1 62	31 1	6 89	22 2	1 34	-10 0	0 27	9 1	0 13
1 13	4 2	0 03	0 5	0	24 0	2 07	-6 6	0 03	1 0	0
14 94	14 0	0 24	28 2	1 51	26 8	0 65	-19 2	0 40	5 3	0

TABLE C4 5

Activity 2 vs Activity 3 Occupations 14-94 only Excess frequency as in Table C4 4 of high values among men of Activity 2

SAMPLE	REL. WT Excess	Chi²	Σ SKINFOLDS Excess	Chi²	SYST B P Excess	Chi²	DIAST B P Excess	Chi²	CHOLESTEROL Excess	Chi²
East Finland	51 1	8 32	71 9	16 44	9 1	0 22	7 1	0 11	11 1	0 38
West Finland	51 2	9 88	47 2	8 55	11 5	0 44	37 2	5 55	-7 9	0 18

TABLE C4 6

Occupation 1 13 vs 14 94 Excess frequency as in Table C4 4 of high values among men in Occupations 1 13 expressed as % of expectation from total numbers of men in Occupations 1 13 + 14 94

ACTIVITY	REL. WT Excess	Chi²	Σ SKINFOLDS Excess	Chi²	SYST B P Excess	Chi²	DIAST B P Excess	Chi²	CHOLESTEROL Excess	Chi²
East Finland										
1+2	31 5	7 35	35 3	12 61	19 8	0 91	10 9	0 31	14 6	0 63
1	9 0	0 20	24 4	5 16	14 9	0 23	-23 7	1 32	11 8	0 13
2	51 1	7 81	37 9	4 45	30 6	0 70	0	0	-16 7	0 25
West Finland										
1+2	36 6	4 52	52 0	10 56	12 1	0 11	9 4	0 08	26 2	0 86
1	12 7	0 54	21 2	3 04	9 4	0	13 6	0 16	13 6	0 16
2	66 7	1 98	76 5	2 44	78 6	2 13	25 0	0 05	30 4	0 03

Probabilities p associated with chi square values 2 71 p = 0 10 3 84 p = 0 05 5 41 p 0 02 6 64 p 0 01 10 83 p 0 001

C4 7 which gives the numbers of men classed by smoking habits and distributed as below or above the age-specific medians for all men in the designated sample In both samples the tendency of the non-smokers to be more often relatively heavier and fatter than the rest of these Finns is very pronounced while the heavy smokers have a marked but less striking tendency in the opposite direction

The non-smokers in both areas also differ in tending to have higher blood pressure and this is clear in both systole and diastole Again the heavy smokers as well as "other" smokers show the opposite tendency Serum cholesterol concentration tends to be somewhat low in the non-smokers while both heavy and "other" smokers consistently tend to the opposite distribution

Except for serum cholesterol all of these differences between non-smokers and either heavy or "other" smokers are statistically significant The difference in serum cholesterol concentration is not statistically significant when heavy or "other" or all smokers are compared with non-smokers When heavy smokers are compared with "other" smokers no significant differences are found

Electrocardiographic Findings

Tables C4 8, C4 9 C4 10 and C4 11 summarize the electrocardiographic findings both in rest and after the final exercise test Thirteen men showed clear evidence of old myocardial infarction but there is no difference between the two areas of Finland in this small number the age-corrected rates being 8 6 and 7 4 per 1 000 men for East and West Finland respectively There were no cases of complete heart block and only 5 cases of left bundle branch block (2 in East 3 in West Finland) High amplitude R waves (left type Code III 1) and sinus bradycardia (Code VIII 8) were fairly common in both areas but the samples did not differ significantly in the prevalence of either of these findings

The post-exercise ECGs in Finland showed fewer major new abnormalities than the average of all samples studied This may reflect the high degree of physical training noted as being almost the rule in the Finnish men

Prevalence of Hypertension versus Other Variables

By any ordinary criterion of blood pressure the prevalence of hypertension in East Finland was much greater than in West Finland Table C4 12 gives the prevalence with two criteria of diastolic blood pressures With either criteria the difference is statistically highly significant and is consistent at all ages The prevalence of hypertension was significantly more common in East Finland and less common in West Finland than among men in all 18 samples in these cooperative studies

The distributions of the hypertensive Finns (95 mm or more in the 5th phase of diastole) into age- and area specific decile classes of relative body weight Σ skinfolds and serum cholesterol concentration are shown in Figures C4.3 and C4 4 Note that in these graphs absence of a relationship would be represented by points randomly distributed about a horizontal straight line In East Finland the frequency of hypertension tends to rise at the upper end of the distributions of relative body weight but this tendency is much more evident in West Finland where the top 10 per cent (decile 10) of the men in relative weight are about four times more prone to be hypertensive than the men in the first eight decile classes A somewhat similar but less marked relationship is shown between hypertension prevalence and body fatness and again the picture is

TABLE C4 7

Smoking Number of men in Finland below (LOW) and above (HIGH) the age-specific medians for age and area, of measured variables, classed according to smoking habits HEAVY = 20 or more OTHER = 1-19 cigarettes daily

VARIABLE	SAMPLE	NON SMOKERS		HEAVY		OTHER	
		LOW	HIGH	LOW	HIGH	LOW	HIGH
Relative Weight	E Finland	94	160	133	117	176	117
" "	W "	115	241	72	52	230	124
Σ Skinfolds	E Finland	82	175	147	109	179	123
	W "	119	246	81	46	226	137
Systolic B P	E Finland	116	137	136	117	153	149
	W	159	206	69	58	200	163
Diastolic B P	E Finland	106	147	146	117	162	139
'	W '	145	220	73	54	209	154
Serum Cholesterol	E Finland	138	119	123	133	147	154
'	W '	191	173	59	68	177	185

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TABLE C4 9

KARELIA FINLAND

FREQUENCY OF POST EXERCISE ELECTROCARDIOGRAPHIC FINDI^GS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40 44 (201)	45 49 (220)	50 54 (170)	55 59 (138)
Exercise tests not made or	X 1				
incomplete	X 2	6 (29 0)	18 (75 6)	27 (137 1)	34 (197 7)
S T Depression post exercise (none at rest)	XI				
S T J 1 mm or more horiz or downward segment	1	0	0	0	1 (7 2)
S T J 0 5 1 mm horiz or downward segment	2	1 (5 0)	3 (13 6)	2 (11 8)	0
No S T J plus segment downward	3	0	0	0	0
S T J 1 mm or more upward segment	4	3 (14 9)	1 (4 5)	3 (17 6)	5 (36 2)
T Wave Negativity post exercise (none at rest)	XII				
5 mm or more	1	0	0	0	0
1 to 5 mm	2	0	0	0	0
0 ± 1 mm	3	0	1 (4 5)	3 (17 6)	1 (7 2)
Arrhythmias post exercise (none at rest)	XV 1	0	2 (9 1)	2 (11 8)	5 (36 2)
Technically poor post exercise ecords	XI 8	1 (5 0)	1 (4 5)	1 (5 9)	0

FREQUENCY OF CERTAIN ECG FINDI^GS A^D COMBINATIO S OF CLI^ICAL IMPORT

At Rest					
Large Q Wav s	I 1	1 (4 8)	2 (8 4)	1 (5 1)	3 (17 4)
Lesser Q Waves with Negative T Waves	I 2 3 + V 1 2	1 (4 8)	1 (4 2)	0	2 (11 6)
Deeply N gative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	3 (14 5)	10 (42 0)	4 (20 3)	8 (46 5)
S T Depression as sole anomaly	IV 1 4 only	0	0	1 (5 1)	1 (5 8)
High Amplitude R with S T Depres ion	III 1 + IV 1 4	2 (9 7)	2 (8 4)	2 (10 2)	6 (34 9)
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduct on Defect	VII 1 2 4	1 (4 8)	1 (4 2)	2 (10 2)	1 (5 8)
Arrhythmias	VIII 2 6	1 (4 8)	2 (8 4)	1 (5 1)	3 (17 4)
Post ex c se					
S T D p ession as sole anomaly	XI 1 4 only	2 (10 0)	2 (9 1)	2 (11 8)	3 (21 7)
N gative T as sol anomaly	XII 1 3 only	0	0	0	0
Ventricula Conduction D fect a ol anomaly	XIV 1 2 4 only	0	0	0	0
A hythmias as sol anomaly	XV 1 only	0	1 (4 5)	1 (5 9)	1 (7 2)

TABLE C4 8

KARELIA FINLAND

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code		AGE GROUP (Number of Men) 40-44 (207)	45-49 (238)	50-54 (197)	55 59 (172)
Total with reportable ECG Items	I - IX		92 (444 4)	117 (491 6)	107 (543 1)	105 (610 5)
Q Waves	I	1	1 (4 8)	2 (8 4)	1 (5 1)	3 (17 4)
		2	2 (9 7)	1 (4 2)	2 (10 2)	2 (11 6)
		3	0	1 (4 2)	0	3 (17 4)
Axis Deviation	II					
Left		1	4 (19 3)	6 (25 2)	10 (50 8)	4 (23 3)
Right		2	0	0	0	0
High Amplitude R Waves	III					
Left type		1	33 (159 4)	38 (159 7)	40 (203 0)	35 (203 5)
Right type		2	0	0	0	0
S-T Depression (rest)	IV					
S-T - J 1 mm or more horiz or downward segment		1	0	2 (8 4)	2 (10 2)	5 (29 1)
S T - J 0 5 - 1 mm horiz or downward segment		2	2 (9 7)	3 (12 6)	3 (15 2)	6 (34 9)
No S T-J plus segment downward		3	0	0	0	4 (23 3)
S T J 1 mm or more, upward segment		4	0	0	0	0
T Wave Negativity (rest)	V					
- 5 mm or more		1	0	1 (4 2)	0	2 (11 6)
1 mm to -5 mm		2	1 (4 8)	6 (25 2)	3 (15 2)	14 (81 4)
0 ± 1 mm		3	7 (33 8)	15 (63 0)	9 (45 7)	12 (69 8)
A V Conduction Defect	VI					
Complete Block		1	0	0	0	0
Partial Block		2	0	0	0	0
P-R over 0 21 second		3	11 (53 1)	9 (37 8)	4 (20 3)	5 (29 1)
Accelerated Conduction		4	0	0	0	1 (5 8)
Ventricular Blocks	VII					
Left Bundle		1	0	1 (4 2)	0	1 (5 8)
Right Bundle		2	1 (4 8)	0	2 (10 2)	0
Incomplete Right Bundle		3	6 (29 0)	3 (12 6)	8 (40 6)	2 (11 6)
Intraventricular Block		4	0	0	0	0
Arrhythmias	VIII					
Premature Beats		1	0	3 (12 6)	4 (20 3)	3 (17 4)
Ventricular tachycardia		2	0	0	0	0
Atrial fibrillation flutter		3	0	1 (4 2)	0	1 (5 8)
Supra-vent tachycardia		4	0	0	0	0
Ventricular rhythm		5	0	0	0	0
A V nodal rhythm		6	1 (4 8)	1 (4 2)	1 (5 1)	2 (11 6)
Sinus tachycardia		7	3 (14 5)	5 (21 0)	5 (25 4)	3 (17 4)
Sinus bradycardia		8	9 (43 5)	14 (58 8)	7 (35 5)	10 (58 1)
Technically poor records	IX	8	0	0	0	0

TABLE C4 11

WEST FINLAND

FREQUENCY OF POST EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40 44 (164)	45 49 (216)	50 54 (226)	55 59 (?03)
Exercise tests not made or incomplete	X 1 X 2	4 (23 8)	7 (31 4)	19 (77 6)	18 (81 4)
S T Depression post exercise (none at rest)	XI				
S T J 1 mm or more horiz or downward segment	1	1 (6 1)	0	1 (4 4)	0
S T J 0 5 1 mm horiz or downward segment	2	1 (6 1)	6 (27 8)	2 (8 8)	2 (9 9)
No S T J plus segment downward	3	0	1 (4 6)	0	2 (9 9)
S T J 1 mm or more upward segment	4	0	2 (9 3)	7 (31 0)	4 (19 7)
T Wave Negativity post exercise (none at rest)	XII				
5 mm or more	1	0	0	0	0
1 to 5 mm	2	1 (6 1)	0	0	1 (4 9)
0 + 1 mm	3	2 (12 2)	5 (23 1)	5 (22 1)	4 (19 7)
Arrhythmias post exercise (none at rest)	XV 1	3 (18 3)	8 (37 0)	9 (39 8)	7 (34 5)
Technically poor post exercise r cords	XI 8	4 (24 4)	3 (13 9)	3 (13 3)	5 (24 6)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

ECG FINDING	ECG Code	40 44	45 49	50 54	55 59
At Rest					
Larg Q Waves	I 1	2 (11 9)	0	1 (4 1)	3 (13 6)
Lesser Q Waves with Negative T Waves	I 2 3 + V 1 2	0	0	0	0
De ply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	5 (29 8)	4 (17 9)	3 (12 2)	9 (40 7)
S T D pression as sole anomaly	IV 1 4 only	0	0	1 (4 1)	0
High Amplitude R with S T Depression	III 1 + IV 1 4	4 (23 8)	0	5 (20 4)	1 (4 5)
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2 4	3 (17 9)	2 (9 0)	4 (16 3)	3 (13 6)
Arrhythmias	VIII 2 6	0	3 (13 5)	1 (4 1)	3 (13 6)
Post exercise					
S T Depression as sole anomaly	XI 1 4 only	1 (6 1)	4 (18 5)	5 (22 1)	2 (9 9)
Negative T as sole anomaly	XII 1 3 only	0	3 (13 9)	4 (17 7)	1 (4 9)
V nt i ula Conduction Defect as sol anomaly	XIV 1 2 4 only	0	0	0	0
Arrhythmias as sol anomaly	XV 1 only	1 (6 1)	4 (18 5)	5 (22 1)	3 (14 8)

TABLE C4 10

WEST FINLAND

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (168)	45-49 (223)	50-54 (245)	55 59 (271)
Total with reportable ECG Items	I - IX	77 (458 3)	96 (430 5)	118 (481 6)	119 (538 5)
Q Waves	I 1	2 (11 9)	0	1 (4 1)	3 (13 6)
	2	1 (6 0)	2 (9 0)	1 (4 1)	0
	3	0	2 (9 0)	1 (4 1)	2 (9 0)
Axis Deviation	II				
Left	1	7 (41 7)	6 (26 9)	15 (61 2)	11 (49 8)
Right	2	1 (6 0)	0	0	0
High Amplitude R Waves	III				
Left type	1	27 (160 7)	28 (125 6)	44 (179 6)	40 (181 0)
Right type	2	0	1 (4 5)	2 (8 2)	1 (4 5)
S-T Depression (rest)	IV				
S-T - J 1 mm *or more* horiz or downward segment	1	2 (11 9)	0	2 (8 2)	1 (4 5)
S-T - J 0 5 - 1 mm horiz or downward segment	2	2 (11 9)	0	5 (20 4)	3 (13 6)
No S-T J plus segment downward	3	1 (6 0)	0	2 (8 2)	1 (4 5)
S T - J 1 mm or more, upward segment	4	0	0	0	1 (4 5)
T-Wave Negativity (rest)	V				
- 5 mm or more	1	0	0	1 (4 1)	0
- 1 mm to -5 mm	2	5 (29 7)	0	4 (16 3)	3 (13 6)
0 ± 1 mm	3	7 (41 7)	8 (35 9)	7 (28 6)	17 (76 9)
A-V Conduction Defect	VI				
Complete Block	1	0	0	0	0
Partial Block	2	0	2 (9 0)	0	0
P R over 0 21 second	3	1 (6 0)	6 (26 9)	12 (49 0)	4 (18 1)
Accelerated Conduction	4	0	0	1 (4 1)	0
Ventricular Blocks	VII				
Left Bundle	1	0	0	1 (4 1)	2 (9 0)
Right Bundle	2	3 (17 9)	2 (9 0)	3 (12 2)	1 (4 5)
Incomplete Right Bundle	3	2 (11 9)	2 (9 0)	7 (28 6)	6 (27 1)
Intraventricular Block	4	0	0	0	0
Arrhythmias	VIII				
Premature Beats	1	2 (11 9)	2 (9 0)	2 (8 2)	5 (22 6)
Ventricular tachycardia	2	0	0	0	0
Atrial fibrillation flutter	3	0	1 (4 5)	1 (4 1)	2 (9 0)
Supra-vent tachycardia	4	0	0	0	0
Ventricular rhythm	5	0	0	0	0
A V nodal rhythm	6	0	2 (9 0)	0	1 (4 5)
Sinus tachycardia	7	4 (23 8)	1 (4 5)	2 (8 2)	3 (13 6)
Sinus bradycardia	8	7 (41 7)	6 (26 9)	8 (32 7)	10 (45 2)
Technically poor records	IX 8	0	0	0	0

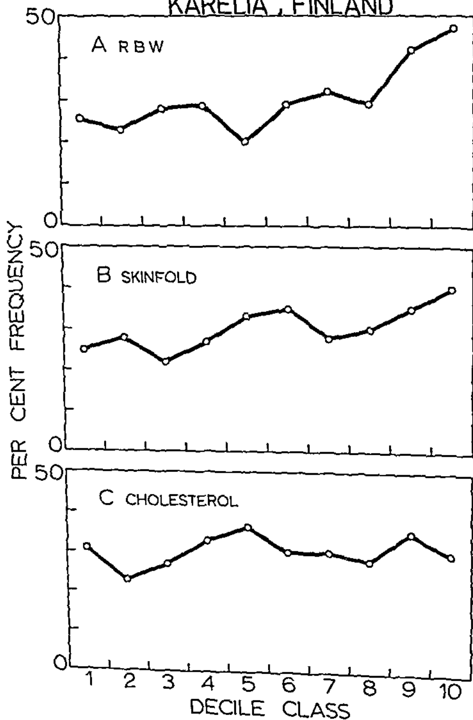

KARELIA, FINLAND
A RBW
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

TABLE C4 12

Prevalence of diastolic hypertension (95 or more, 100 or more mm Hg, fifth phase) among men classed by age Percentage of men in East and West Finland who are hypertensive, compared with the average for all 18 samples of men

SAMPLE	40-44		45-49		50-54		55-59	
	95 mm	100 mm	95 mm	100 mm	95 mm	100 mm	95 mm	100 mm
East Finland	21 8	13 1	27 2	17 4	35 5	23 8	38 2	25 3
West Finland	8 3	4 2	5 8	3 6	14 7	10 2	13.5	7 2
Mean, 18 samples	13 6	7 9	15 6	8 9	20 9	13 5	21 5	13 8

TABLE C4 13

Prevalence of overweight (110 or more and 120 or more per cent of "standard" average for height and age) Percentage of men in East and West Finland classed by age who are overweight compared with the average for all 18 samples of men

SAMPLE	40-44		45-49		50-54		55-59	
	110%	120%	110%	120%	110%	120%	110%	120%
East Finland	10 7	3 9	10 9	3 5	13 9	3 6	10 1	4 8
West Finland	15 9	8 5	19 9	6 0	18 5	7 1	13 8	5 0
Mean, 18 samples	20 9	8 4	19 4	6 9	18 1	6 7	16 8	7 3

more marked in West than in East Finland In neither area considered alone is the prevalence of hypertension significantly related to the serum cholesterol level except perhaps for the indication in West Finland that the men with the highest cholesterol values (decile 10) are more prone to hypertension than the men with the lowest values for cholesterol (decile 1) In West Finland out of 85 men in cholesterol decile class 10 there were 18 cases of hypertension but the first decile class only 4 out of 85 men were hypertensive the difference has very high significance (chi square=22 98) If East and West Finland are combined the prevalence of hypertension is clearly related to the serum cholesterol level but this merely reflects the fact that both hypertension and hypercholesterolemia are more frequent in East than in West Finland

Prevalence of Overweight versus Other Variables

Table C4 13 shows the prevalence of overweight by two criteria of relative body weight Overweight defined as body weight 110 per cent or more above the U S Medico Actuarial average for height and age is more common in West than in East Finland the prevalence rates being 17 and 11 per cent respectively The difference 54 5 per cent more frequent overweight in West than in East Finland is highly significant (chi square = 10 91 p = 0 001)

The West Finns tend to be a little less often overweight than the men in all 18 samples but the difference is in significant The East Finns however are much less often overweight and the difference from the total population of men is highly significant

The distributions of the overweight Finns (110 or more per cent of the standard" average for height and age) into age and area specific decile classes of the distributions for all Finns of blood pressure and serum cholesterol are shown in Figures C4 5 and C4 6 Overweight prevalence is not related to serum cholesterol level in East Finland but in West Finland there is a trend for overweight prevalence to increase with rising serum cholesterol level Comparing the men in the below-vs above median cholesterol values the numbers of overweight men are 58 and 86 respectively and the non-overweights number 336 and 338 chi-square = 6 098 and p = less than 0 02

In both areas the frequency of overweight rises with both systolic and diastolic blood pressure and the trend is highly significant

Summary

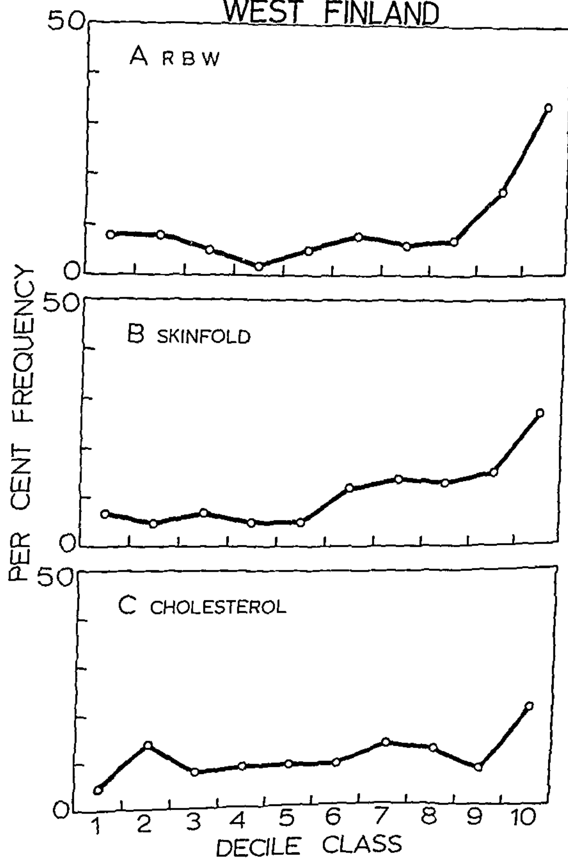
In two rural areas of East and of West Finland 98 per cent of all men aged 40—59 (N = 1677) were examined Three fourths of these men were engaged in heavy physical work on small farms and in logging only 10 per cent were sedentary or engaged only in light physical activity

These men tended to be thin and to have very high serum cholesterol values especially in East Finland The less active men and those in the higher socioeconomic class tended to have the highest relative body weights and Σ skinfolds Neither blood pressure nor serum cholesterol tended to be related to physical activity or socio economic status

Most of these men smoked cigarettes The non smokers included unduly large proportions of the relatively heavy obese men and men with high blood pressure

Both areas tended to have a relatively high frequency of electrocardiographic abnormalities this was most pronounced in East Finland

The prevalence of hypertension tended to increase with increasing relative


WEST FINLAND
A RBW
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

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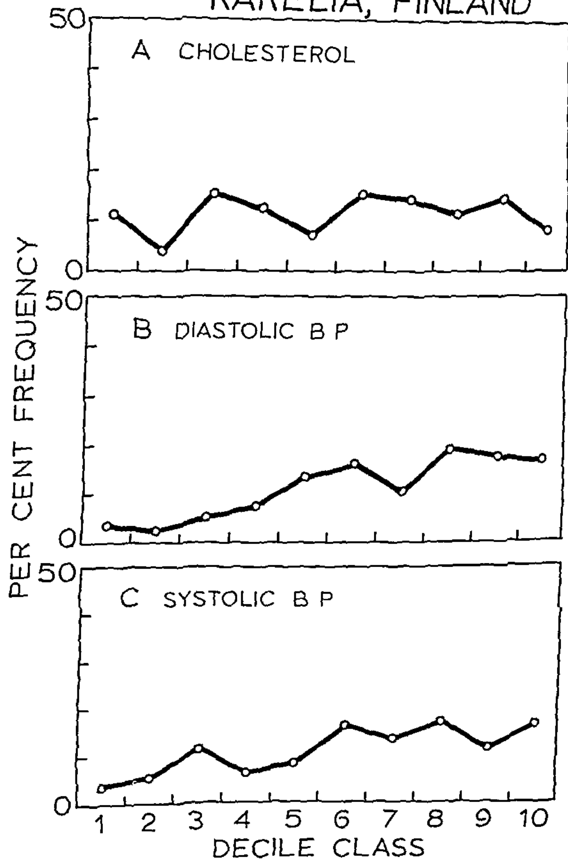
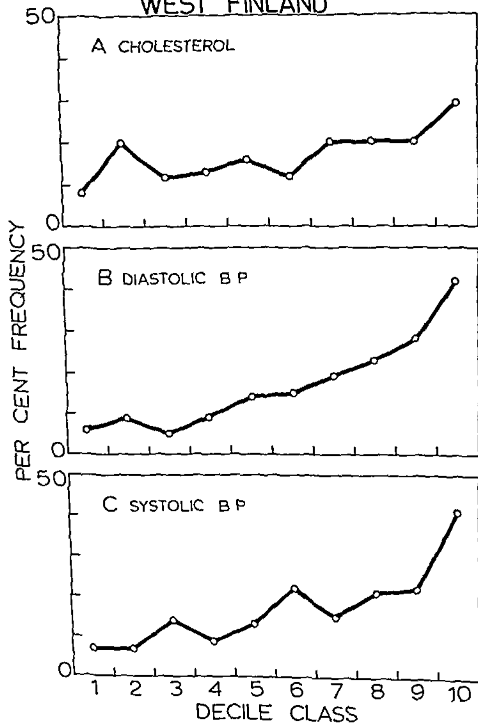


KARELIA, FINLAND
A CHOLESTEROL
B DIASTOLIC B P
C SYSTOLIC B P
PER CENT FREQUENCY
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

Figure C4 5


WEST FINLAND
50
0
A CHOLESTEROL
50
0
B DIASTOLIC B P
50
0
C SYSTOLIC B P
PER CENT FREQUENCY
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

body weight and Σ skinfolds especially in West Finland The prevalence of hypertension appeared to be unrelated to serum cholesterol concentration in either area

Overweight was uncommon in East Finland somewhat more common in West Finland In both areas but especially in West Finland the prevalence of overweight rose with increasing blood pressure In West Finland but not in East Finland the prevalence of overweight rose with increasing serum cholesterol concentration

Acknowledgments

The research team in 1959 in East and West Finland included Drs Gunnar Blomqvist (Stockholm) Veikko Kallio (Turku) Martti J Karvonen Esko Orma Sven Punsar (all of Helsinki) Pentti Rautaharju (Halifax) Juha Takkunen Mr A O Heinonen and Nurse Mrs Anja Valve (all of Helsinki) Drs Ratko Buzina (Zagreb) Louisa M Dalderup (Amsterdam) Ian T T Higgins (then Cardiff now of Pittsburgh) and Elisabeth Marler contributed their experience at the beginning phase of the study

Establishing the roster of men and securing their participation was the responsibility of two Health Nurses Mrs Impi Lavikainen in the East and Mrs Kirsti Kuisma in the West

The local physicians Drs Tauno Koistinen and Kaarlo Hallantie in the East Dr Ahti Alho and the late Dr Väinö Westerback in the West were helpful in many ways

Mr Yrjö Rautanen M A at the Institute of Occupational Health Helsinki was responsible for the transfer of serum samples to the central laboratory and did much work in checking the procedures used

Prof Leo Noro Director of the Institute of Occupational Health placed staff members and facilities of the Institute at the disposal of the study

The participation of Finland in the collaborative investigation was largely due to the stimulus of Prof Pauli Soisalo then President of the Board of the Finnish Heart Association

C5 THE TOWN OF ZUTPHEN, THE NETHERLANDS

by F S P van Buchem and L M Dalderup

Introduction

Zutphen has long been a small commercial town a center of commerce and traffic of a farming district in the eastern part of the Netherlands The climate is typical of the lowlands near the North Sea that is to say it is temperate and moist In modern times manufacturing has become increasingly important with a particularly strong development after the second world war Today there are among others factories producing machinery ready-made clothing and for processing iron and leather printing and book binding establishments rag grading and packing plants Besides light industry and the activities of a retail market center Zutphen is notable as a center for secondary and technical education for a large district The two hospitals of the town have a full staff of specialists including three specialists in internal medicine The population numbers about 25 000

Zutphen was chosen as a center for epidemiological research on athero sclerosis because it is a town of suitable size with a very stable population who had shown willingness to coop erate in an earlier somewhat simila medical survey The population registry of Zutphen on January 1 1960 contained about 2 300 men then aged 40 through 59 years Because only about 1 000 men of those ages could be included in the study 4 out of every 9 names were randomly selected from the alphabetical registry Seventy per cent of these men responded favorably to a written invitation and the remaining 30 per cent were personally visited in the attempt to recruit them

In the summer of 1960 a total of 907 men were examined representing 83 4 per cent of those invited When the studies were repeated in 1961 and 1962 another 10 invitees came in bringing the total to 917 men and 84 3 per cent coverage in the full examination The cooperation of the local physicians made it possible to obtain information about the state of health of all but 7 of the men who were unwilling to co-operate

The examinations in 1960 were carried out by a team headed by a professor of internal medicine which included 3 internists 2 general practitioners an ophthalmologist who were assisted by technicians and nurses

In addition to the standard items in the protocol common to all of the areas in this cooperative study the work at Zutphen in 1960 included detailed ophthalmological examination and fluoroscopy of the chest These latter

items will be considered in separate reports

The present statistical analysis concerns 878 men whose records were complete for most items and who were 40 through 59 years of age at the time of the examinations in 1960

Age, Physical Activity and Occupation

Table C5 1 gives the distribution of men by age into the three classes of habitual physical activity In regard to age there is a notable deficit of men aged 40—44 in the sample presumably reflecting losses to the Zutphen population of the younger men related to World War II and its aftermath of migration The men aged 40—44 in 1960 were aged 25—29 at the end of the war in 1945 Except for the U S A a relative deficiency of men in this youngest age class was noted in all of the other samples in this cooperative study

Few of the middle-aged men in Zutphen are engaged in heavy work but there is no evidence for a withdrawal from heavy manual labor with advancing age the *highest* percentage of men in heavy work is in the oldest age group The occupational distribution of the Zutphen men is given in Table C5 2 It is notable that a third of the sample are professional men or are engaged in business or clerical jobs The occupational data indicate that a high proportion of the middle-aged men in Zutphen are in 'white collar" jobs or in jobs involving a considerable degree of skill Agricultural pursuits of one kind or another which once occupied a substantial proportion of men in Zutphen was represented in 1960 by only 2 5 per cent of the men in the sample Both in regard to physical activity and occupation the distribution of the men in Zutphen is greatly different from all the other general population samples in this cooperative study the other samples being dominated by heavy physical activity and by farmers

Distribution of the Measured Variables

Table C5 3 gives the median values of the men classed by age for relative body weight the sum of the skinfolds blood pressure and serum cholesterol Table C5 3 also gives these medians as percentages of the average medians for the men in all 18 samples in this cooperative study The cumulative frequency distributions of these variables are shown in Figure C5 1 Details of the distributions are given in the Appendix

In this Zutphen material there was no significant age trend in height skinfold thickness or serum cholesterol so all ages 40—59 were combined to provide the cumulative frequency distributions of these variables in Figure C5 1 Relative body weight and both systolic and diastolic blood pressure showed significant age trends For these three variables the heavy line is for ages 40—49 the light line is for ages 50—59 In Figure C5 1 the ordinate is on a probability scale The deviation of the cumulative frequencies from a straight line is obvious for blood pressure at ages 50—59 but serum cholesterol and Σ skinfolds also depart somewhat from a normal Gaussian distribution

The men of Zutphen are relatively tall being exceeded in height only slightly by the U S railway executives who are the tallest group among the 18 samples Though they tend to have slightly higher relative body weights than the men in most of the other samples they are not so much inclined to overweight as the men in Crevalcore and Rome Italy or any of the U S samples Their position in regard to body fatness is similar to that for rela-

TABLE C5 1

Zutphen men in 1960, classed by age and physical activity (1 = sedentary, 2 = moderately active 3 = very active)

AGE	TOTAL MEN	% IN ACTIVITY 1	2	3
40-44	181	24 3	66 9	8 8
45-49	237	17 8	74 2	8 1
50-54	235	24 3	64 7	11 1
55-59	225	30 7	52 4	16 9
All ages	878	24 1	64 6	11 3

TABLE C5 2

Zutphen men 1960 classed by occupation

OCCUPATION	CODE	%	OCCUPATION	CODE	%
Professional	1-10	5 3	Building trades	54-61	11 0
Business etc	11-15	17 5	Metal work	62-65	8 5
Foreman	16-22	4 7	Agriculture	66-69 71-75	2 5
Clerical	23-26	10 5	Factory work	78-80	5 5
Protection	27-30	3 0	Services	81-87	2 6
Food Handlers	31-39	5 8	General labor	88, 89	3 4
Skilled light crafts	40-44	5 2	Miscellaneous	90-94	7 3
Transportation	45-53	6 3	Not working	95-98	0 8

TABLE C5 3

Medians for Zutphen men classed by age and these values as percentages of the averages of the medians for all 18 samples of men

VARIABLE	MEDIAN VALUES 40-44	45-49	50-54	55-59	MEDIAN % OF AVERAGE 40-44	45-49	50-54	55-59
Height (cm)	175	175	174	172	103 1	103 5	103 4	102 6
Relative Wt (%)	99	97	97	97	100 9	100 8	101 9	103 1
Σ Skinfolds (mm)	24	23	24	22	113 2	112 5	115 9	110 6
Systolic B P (mm Hg)	140	140	140	145	106 9	105 3	102 2	103 1
Diastolic B P '	90	90	90	88	111 1	110 6	107 9	104 4
Serum Chol (mg %)	233	235	227	226	112 9	113 4	108 7	109 4

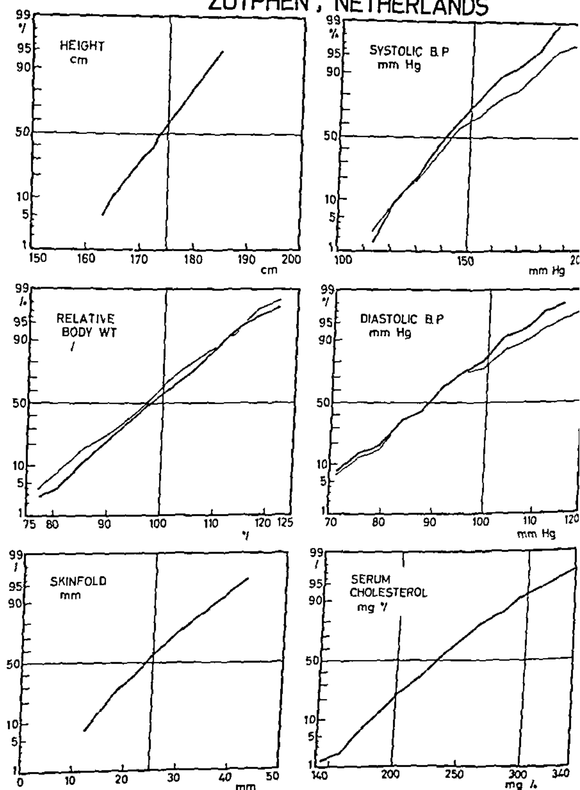

ZUTPHEN , NETHERLANDS
HEIGHT
cm
SYSTOLIC B.P
mm Hg
RELATIVE
BODY WT
%
DIASTOLIC B.P
mm Hg
SKINFOLD
mm
SERUM
CHOLESTEROL
mg %

Figure C5 1

tive body weight all of the U S samples tend to be much fatter and the Rome railway employees are slightly fatter than the men of Zutphen

In general the men of Zutphen tend to have somewhat higher blood pressures than the men in any of the other areas except in Karelia (East Finland) Finally the serum cholesterol concentration tends to be relatively high in these men but not as high as in the U S railway employees and far lower than in the men in Finland In a broad classification of the 18 population samples the men of Zutphen would be grouped with the men in Finland and in the U S A in the high serum cholesterol category

Smoking Habits

In regard to smoking habits the men of Zutphen differ from the men in all of the other 17 samples in this cooperative study in that many of them smoke pipes and cigars these are infrequently used in the other populations Still three quarters (74 7 per cent) of these men of Zutphen smoke cigarettes though only a few (10 6 per cent) could be classed as heavy cigarette smokers i e men who regularly smoke 20 or more cigarettes daily Only 7 6 per cent of the Zutphen men never smoked cigarettes Table C5 4 gives the data

As in most of the other samples it was observed that the non cigarette smokers tended to be relatively heavier and fatter than the cigarette smokers Though the non-cigarette smokers represented only 25 3 per cent of the sample they accounted for 35 1 per cent of the men in the top 20 per cent for relative body weight and 37 6 per cent of the top 20 per cent in the sum of the skinfolds There was no significant difference between the cigarette smokers and the non cigarette smokers in their distribution in regard to blood pressure or serum cholesterol Data are summarized in Table C5 5

The heaviest cigarette smokers were not notable in regard to blood pressure or serum cholesterol but curiously they too like the non cigarette smokers tended to overweight and obesity Though only representing 10 7 per cent of all the men they accounted for 16 1 and 15 0 per cent of the top 20 per cent of all men in relative weight and sum of skinfolds respectively These figures indicate excesses of 51 9 and 41 5 per cent respectively of cases of overweight and of obesity among the heavy cigarette smokers

Electrocardiographic Findings

The electrocardiographic data from recordings at rest are summarized in Table C5 6 which gives numbers of cases and rates per 1 000 men of findings of abnormalities in terms of the classification in the Minnesota Code (Blackburn *et al* 1960) As expected the prevalence of ECG abnormality increased with age in substantially all items An interesting exception is the prevalence of sinus tachycardia in rest which steadily decreased with age

The most common single abnormalities in rest were left axis deviation (Code II 1) tall R waves (Code III 1) flat or slightly negative T wave (Code V 3) and sinus tachycardia (Code VIII 7) with all-ages prevalences of 39 9 43.3 36 5 and 53 6 cases per thousand respectively Q wave abnormality was relatively frequent The most definite sign of previous myocardial infarction Code I 1 was shown by 8 men (9 1 per thousand) for men 55—59 the rate of this finding was 22 2 per thousand

The post-exercise ECG recorded for 97 7 per cent of the men provided a moderate yield of additional abnormalities particularly of S-T depression

TABLE C5 4

Cigarette smoking habits of men of Zutphen Percentage of men who never smoked, who had stopped who smoked 1-9 10-19, 20 or more cigarettes daily at the time of their examination

SAMPLE	AGE	NEVER	QUIT	1-9	10-19	20 OR MORE
Zutphen	40-44	6 1	11 2	27 4	39 7	15 6
"	45-49	6 4	11 5	32 5	36 8	12 8
"	50-54	6 4	24 3	30 6	31 9	6 8
"	55-59	11 3	22 6	30 8	26 7	8 6
"	40-59	7 6	17 7	30 5	33 5	10 7

TABLE C5 5

Smoking Number of men in Zutphen, Netherlands below (LOW) and above (HIGH) the age-specific medians, for age and area, of measured variables, classed according to smoking habits HEAVY = 20 or more, OTHER = 1-19 cigarettes daily

VARIABLE	SAMPLE	NON-SMOKERS		HEAVY		OTHER	
		LOW	HIGH	LOW	HIGH	LOW	HIGH
Relative Weight	Zutphen	98	122	43	49	294	262
Σ Skinfolds	"	86	134	44	49	303	253
Systolic B P	"	105	115	44	49	284	271
Diastolic B P	"	93	127	44	48	298	257
Serum Cholesterol	"	110	103	34	57	268	253

TABLE C5 6

ZUTPHEN NETHERLANDS

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code		AGE GROUP (Number of Men) 40 44 (180)	45-49 (237)	50-54 (235)	55 59 (225)
Total with reportable ECG Items	I IX		76 (422 2)	109 (459 9)	106 (451 1)	106 (471 1)
Q Waves	I	1	0	0	3 (12 8)	5 (22 2)
		2	3 (16 7)	3 (12 7)	2 (8 5)	6 (26 7)
		3	3 (16 7)	1 (4 2)	2 (8 5)	5 (22 2)
Axis Deviation	II					
Left		1	3 (16 7)	11 (46 4)	7 (29 8)	14 (62 2)
R ght		2	1 (5 6)	0	0	1 (4 4)
High Amplitude R Waves	III					
Left type		1	6 (33 3)	10 (42 2)	9 (38 3)	13 (57 8)
Right type		2	0	0	0	1 (4 4)
S T Depression (rest)	IV					
S T J 1 mm or more horiz or downward segment		1	0	0	4 (17 0)	6 (26 7)
S T J 0 5 1 mm horiz or downward s gment		2	0	4 (16 9)	2 (8 5)	3 (13 3)
No S T J plus segment downward		3	1 (5 6)	2 (8 4)	4 (17 0)	2 (8 9)
S T J 1 mm or more upward segment		4	2 (11 1)	2 (8 4)	1 (4 3)	1 (4 4)
T Wave Negativity (rest)	V					
5 mm or more		1	0	0	0	1 (4 4)
1 mm to 5 mm		2	0	0	9 (38 3)	6 (26 7)
0 ± 1 mm		3	5 (27 8)	5 (21 1)	8 (34 0)	14 (62 2)
A V Conduction Defect	VI					
Compl te Block		1	0	0	0	0
Partial Block		2	0	0	0	0
P R over 0 21 second		3	2 (11 1)	2 (8 4)	4 (17 0)	5 (22 2)
Ac elerated Conduction		4	0	0	0	0
Ventricular Blocks	VII					
Left Bundle		1	0	0	0	3 (13 3)
Right Bundle		2	2 (11 1)	2 (8 4)	2 (8 5)	3 (13 3)
Incomplete Right Bundle		3	2 (11 1)	1 (4 2)	3 (12 8)	4 (17 8)
Intrav ntricular Block		4	5 (27 8)	2 (8 4)	0	2 (8 9)
Arrhythm as	VIII					
Prematu e Beat		1	0	2 (8 4)	1 (4 3)	3 (13 3)
Ventricular tachycardia		2	0	0	0	0
Atr al fibrillation flutter		3	0	1 (4 2)	2 (8 5)	2 (8 9)
Sup a vent tachycardia		4	0	0	0	0
V ntr cular rhythm		5	0	0	0	0
A V nodal rhythm		6	0	0	0	0
S nus tachycardia		7	14 (77 8)	13 (54 9)	11 (46 8)	9 (40 0)
Sinus b adycard a		8	1 (5 6)	2 (8 4)	2 (8 5)	3 (13 3)
Technically poor records	IX	8	0	1 (4 2)	3 (12 8)	0

where none was present in rest The data are given in Table C5 7 In rest 34 cases of S-T depression were observed, 44 more cases were noted post-exercise and in 13 of these the response was that often called 'ischemic" (Code IV, 1, 2, 3) Arrhythmias were observed post-exercise in 13 men who had not shown arrhythmias in rest

Table C5 7 also shows the prevalence of certain ECG findings including combinations that are commonly considered to be of clinical import The only combination of ECG abnormalities that adds materially to the prevalence of clinical import is tall R wave plus S-T depression there were 8 cases of this combination

Prevalence of Hypertension

Table C5 8 shows the prevalence in Zutphen of hypertension specified according to four different criteria By any criterion the men of Zutphen have a high prevalence of elevated blood pressure Among the 18 population samples in the present cooperative study only the men of Karelia (East Finland) match the men of Zutphen in this respect With the relatively conservative criterion of diastolic blood pressure of 100 or more mm Hg about one-fifth of the men of Zutphen have hypertension With the lowest cut-off for hypertension 140 or more mm Hg in systole more than half of the Zutphen men are hypertensive

The prevalence of hypertension in Zutphen is strongly related to relative body weight and to body fatness (Σ skinfolds) as indicated in Table C5 9 Among men above the median for their age of either relative weight or fatness the prevalence of hypertension defined as diastolic blood pressure of 95 or more mm Hg is more than twice that among men below the median The men in the top 20 per cent of the distribution of either relative weight or fatness are about 5 times more prone to hypertension than the men in the bottom 20 per cent of the distribution of these variables

Though there is a slight indication that hypertension increases with increasing serum cholesterol this trend is not statistically significant for the comparison above vs below median cholesterol (chi-square = 1 63) nor for the comparison of the men in the top vs those in the bottom 20 per cent of the cholesterol distribution (chi-square = 3 09)

Prevalence of Overweight

Overweight is subject to definition of course but most investigators would agree that a relative body weight of 10 per cent or more above the average weight for height and age as given in the Medico-Actuarial Tables of 1912 (see Appendix) is definitely overweight For a man aged 50 with height = 170 cm for example a relative weight of 110 per cent on that basis would mean a body weight of 77 7 kg

Among the Zutphen men 13 per cent had relative body weights of 110 per cent or more What were other characteristics of these overweight men? Above it was noted that the prevalence of hypertension was strongly related to relative body weight The reverse analysis is summarized in Table C5 10

In the Zutphen sample the prevalence of overweight is strongly related both to arterial blood pressure and to serum cholesterol concentration The relationship is most marked with diastolic blood pressure Overweight is three times as common among men with above-median than among men with below-median diastolic blood pressure in the top 20 per cent of the diastolic B P distribution the prevalence of overweight is seven times that in the bottom 20 per cent

TABLE C5 7

ZUTPHEN NETHERLANDS

FREQUENCY OF POST EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40 44 (179)	45 49 (234)	50-54 (223)	55 59 (212)
Exercise tests not made or incomplete	X 1 X 2	1 (5 6)	3 (12 7)	12 (51 1)	13 (57 8)
S T Depression post exercise (none at rest)	XI				
S T J 1 mm or more horiz or downward segment	1	1 (5 6)	0	2 (9 0)	5 (23 6)
S T J 0 5 1 mm horiz or downward segment	2	0	1 (4 3)	1 (4 5)	1 (4 7)
No S T J plus segment downward	3	1 (5 6)	1 (4 3)	0	0
S T J 1 mm or more upward segment	4	6 (33 5)	9 (38 5)	7 (31 4)	9 (42 5)
T Wave Negativity post exercise (none at rest)	XII				
5 mm or more	1	0	0	0	0
1 to 5 mm	2	1 (5 6)	2 (8 5)	1 (4 5)	4 (18 9)
0 + 1 mm	3	4 (22 3)	4 (17 1)	3 (13 5)	6 (28 3)
Arrhythmias post exercise (none at rest)	XV 1	1 (5 6)	4 (17 1)	4 (17 9)	4 (18 9)
Technically poor post exercise records	XI 8	6 (33 5)	9 (38 5)	15 (67 3)	9 (42 5)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

At Rest					
Large Q Waves	I 1	0	0	3 (12 8)	5 (22 2)
Lesser Q Waves with Negative T Waves	I 2 3 + V 1 2	0	0	0	0
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	1 (5 6)	1 (4 2)	3 (12 8)	0
S T Depression as sole anomaly	IV 1 4 only	1 (5 6)	0	0	1 (4 4)
High Amplitude R with S T Depression	III 1 + IV 1 4	1 (5 6)	1 (4 2)	2 (8 5)	4 (17 8)
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2 4	7 (38 9)	4 (16 9)	2 (8 5)	8 (35 6)
Arrhythmias	VIII 2 6	0	1 (4 2)	2 (8 5)	2 (8 9)
Post exercise					
S T Depression as sole anomaly	XI 1 4 only	4 (22 3)	5 (21 4)	3 (13 5)	9 (42 5)
Negative T as sole anomaly	XII 1 3 only	0	1 (4 3)	1 (4 5)	4 (18 9)
Ventricular Conduction Defect as sole anomaly	XIV 1 2 4 only	0	0	0	0
Arrhythmias as sole anomaly	XV 1 only	1 (5 6)	3 (12 8)	2 (9 0)	1 (4 7)

TABLE C5 8

Percentage of Zutphen men classed as hypertensive by blood pressure criteria systolic B P 140 or more and 160 or more, diastolic B P 95 or more and 100 or more mm Hg

AGE	SYSTOLIC 140	SYSTOLIC 160	DIASTOLIC 95	DIASTOLIC 100
40-44	54 1	13 8	29 4	19 4
45-49	54 0	19 8	29 1	17 7
50-54	56 2	24 9	30 9	23 2
55-59	63 1	27 6	31 6	22 7

TABLE C5 9

Prevalence (%) of high diastolic B P (95 or more mm Hg) among Zutphen men classed below and above the median and in the bottom and top 20% of all men of same age for the variables indicated

VARIABLE	BOTTOM 20%	BELOW Median	ABOVE Median	TOP 20%
Relative weight	11 5	19 2	41 4	50 5
Σ Skinfolds	11 5	18 0	42 6	53 0
Serum cholesterol	28 0	29 0	33 2	37 5

TABLE C5 10

Prevalence (%) of overweight (110% or more) among Zutphen men classed below and above the median and in the bottom and top 20% of all men of same age for the variables indicated

VARIABLE	BOTTOM 20%	BELOW Median	ABOVE Median	TOP 20%
Systolic B P	8 0	9 2	18 0	26 0
Diastolic B P	4 0	6 2	20 6	28 0
Serum cholesterol	10 0	8 8	17 6	18 5

The prevalence of overweight is about twice as high in the above median systolic B P men as in the below-median men and a similar relationship holds for serum cholesterol In the comparison of the top vs the bottom 20 per cent classes of the distributions however systolic B P may be more important than serum cholesterol All of these differences are statistically highly significant with p = 0 01 or less

Relationships Concerning Occupation and Physical Activity

As noted above the men in Zutphen were classed into three levels of habitual physical activity as well as by occupation The occupations may be grouped into two broad socio economic classes—Code nos 1—13 (professional managerial and business owners) and Code nos 14—94 (all other occupations) The data are suitable for examination of the question as to whether the men so classed differ in their tendency to have high values of the measured variables of relative weight body fatness (Σ skinfolds) arterial blood pressure and serum cholesterol concentration For these purposes low and high values are defined as the bottom and top 30 per cents of the distribution of the values of all Zutphen men in the same age quinquennium

The basic data are set forth in Table C5 11 The bottom 3 lines in Table C5 11 concern physical activity ignoring occupational status In general men with the lowest physical activity (Class 1) tend to be more often overweight over fat and to have higher blood pressure and serum cholesterol values than the other men The moderately active men (Class 2) tend to show the opposite tendency but to a less marked degree The men with the highest physical activity (Class 3) are most often lean and characterized by low serum cholesterol values but they are not remarkable in regard to relative body weight or blood pressure

On the other hand when physical activity is ignored there is an even more striking distinction between men in occupational classes 1—13 and those in all other occupations The men in the upper socio economic class are much more often relatively overweight and obese prone to high blood pressure and to have high serum cholesterol values than the rest of the population It should be noted that the men in occupations 1—13 are generally characterized by low physical activity among a total of 155 men in those occupations 45 8 per cent were in Activity Class 1 and only six could be classed as being very active (Class 3)

The question then arises as to what extent the measured characteristics associated with occupation can be ascribed to physical activity and on the other hand the extent to which socio economic status may be responsible for the differences associated with physical activity Tables C5 12 C5 13 and C5 14 concern these questions It appears that most of the association of low physical activity with high values of these variables is accounted for by socio economic status Some but certainly not all of the association of *high* socio-economic status with high values of these variables *is in* turn accounted for by physical activity

It will be generally agreed that high values of the variables *considered* here are associated with an increased tendency *to develop* coronary heart disease *On this basis* the men at Zutphen who are most at risk are those in the upper *socio-economic* class whose habitual physical activity is low *On the other hand the* men in the lower socio-economic *group* who are most active physically would not appear to represent a remarkably low *risk* group com-

TABLE C5 11

Occupation and physical activity versus measured variables in Zutphen Numbers of men with "Low" and "High" values of the variables "Low" and "High" are the bottom and the top 30 per cents, respectively, of the distributions of all men of the same age

OCCUPATION	PHYSICAL ACTIVITY	RELATIVE WT		Σ SKINFOLDS		SYSTOLIC B P		DIASTOLIC B P		CHOLESTEROL	
		Low	High	Low	High	Low	High	Low	High	Low	High
1-13	Class 1	9	37	9	38	14	23	13	30	12	28
"	" 2	15	31	14	33	28	23	22	25	17	38
"	" 3	0	4	1	0	1	4	0	2	2	2
"	All Classes	24	72	24	71	43	50	35	57	31	68
14-94	Class 1	32	39	31	54	41	49	40	43	38	44
"	" 2	168	125	168	115	144	130	158	144	140	108
'	" 3	32	27	38	17	30	31	27	28	39	25
'	All Classes	232	191	237	186	215	210	225	215	217	177
1 94	Class 1	41	76	40	92	55	72	53	73	50	72
	2	183	156	182	148	172	153	180	169	157	146
	3	32	31	40	17	31	35	27	30	41	27

TABLE C5 12

Activity 1 vs Activity 2 Excess frequency of high values (deciles 8-10) of the variables observed among men of Activity 1 expressed as % of expectation from total numbers of men in Activities 1 plus 2 Also chi-square values for the differences between observed and expected distributions

OCCUPATION	REL WT		Σ SKINFOLDS		SYST B P		DIAST B P		CHOLESTEROL	
	Excess	Chi^2	Excess	Chi^2	Excess	Chi^2	Excess	Chi^2	Excess	Chi^2
Zutphen										
1 94	22 8	5 84	41 3	21 41	20 0	4 26	17 3	3 24	24 8	6 94
1 13	14 9	1 97	13 1	1 61	5 5	0 06	15 8	1 49	-10 8	0 92
14 94	10 2	0 47	44 8	12 47	26 9	4 57	10 5	0 58	29 4	4 64

TABLE C5 13

Activity 2 vs Activity 3 Occupations 14-94 only Excess frequency as in Table C5 12 of high values among men of Activity 2

REL WT		Σ SKINFOLDS		SYST B P		DIAST B P		CHOLESTEROL	
Excess	Chi^2	Excess	Chi^2	Excess	Chi^2	Excess	Chi^2	Excess	Chi^2
2 3	0 38	4 2	1 26	-3 7	1 29	-1 4	0 12	-2 5	0 39

TABLE C5 14

Occupations 1 13 vs 14-94 Excess frequency as in TableC5 12 of high values among men in Occupations 1 13 expressed as % of expectation from total numbers of men in Occupations 1 13 + 14-94

ACTIVITY	REL WT		Σ SKINFOLDS		SYST B P		DIAST B P		CHOLESTEROL	
	Excess	Chi^2	Excess	Chi^2	Excess	Chi^2	Excess	Chi^2	Excess	Chi^2
Zutphen										
1+2	49 1	18 74	47 9	19 23	3 4	0 04	20 9	3 18	46 7	16 82
1	39 1	8 98	18 0	2 43	9 1	3 04	19 5	1 83	8 9	0 31
2	40 9	5 28	15 4	10 01	6 0	0 05	10 6	0 26	74 3	18 40

Probabilities p associated with chi square values 2 71 p = 0 10 3 84 p = 0 05 5 41, p 0 02 6 64 p 0 01 10 83 p - 0 001

pared to the other men in those samples They have a somewhat reduced tendency to hypercholesterolemia but they are not remarkable in either relative body weight or in blood pressure Their chief distinguishing feature is the fact that they are often overweight but not overfat

Prevalence of Hypertension

Table C5 15 shows the prevalence of diastolic hypertension judged by two criteria among men classed by age at Zutphen In general hypertension was common at Zutphen and more prevalent there than in the average of all the samples of men in these studies It is interesting however that there is no age trend over the years 40—59 in the frequency of hypertension at Zutphen

Thirty per cent of all men aged 40—59 at Zutphen would be classed as hypertensive in 95 mm in diastole (fifth phase) is the criterion Figure C5 2 shows the distribution of these hypertensive men into the decile classes of relative body weight Σ skinfolds and serum cholesterol If the prevalence of hypertension were unrelated to these other variables in each case the trend would be random about a horizontal straight line on the graph i e only chance would cause different numbers of men to fall into the different decile classes

At Zutphen the prevalence of hypertension rises sharply with both relative weight and Σ skinfolds substantially the relationship to decile class is an upward-sloping straight line The fattest men (decile 10 in Σ skinfolds) have almost 10 times the prevalence of hypertension of the thinnest men (decile 1) the actual numbers are 49 of 88 and 5 of 88 men respectively

With serum cholesterol a relationship is much less marked and regular However if the men in the top 30 per cent (deciles 8 9 10) of the cholesterol distribution are compared with all the other Zutphen men they prove to have a 19 4 per cent excess of cases of hypertension this is significant with chi square = 5 64 and p = less than 0 02

Prevalence of Overweight

Table C5 16 shows the prevalence of overweight by two relative weight criteria among the men of Zutphen classed by age In general overweight is not very common and it is less frequent at Zutphen than in the average of all samples of men in these studies At Zutphen the frequency of overweight tends to diminish slightly with age from 40 through 59 years

If 110 per cent or more relative body weight is taken as a definition of over weight 13 per cent of all the Zutphen men aged 40—59 are overweight The distributions of those overweight in decile classes of serum cholesterol diastolic blood pressure and systolic blood pressure are shown in Figure C5 3

With increasing blood pressure either systolic or diastolic the prevalence of overweight increases but the relationship tends to be curvilinear especially with systolic blood pressure The top systolic blood pressure class differs sharply from the rest of the distribution in that class 35 6 per cent of the men are overweight and if that class is omitted from the analysis almost no statistically significant relationship remains between overweight and systolic blood pressure

The trend of prevalence of over weight with increasing serum cholesterol is irregular However there is high statistical significance when the top (deciles 8—10) and bottom (deciles 1—3) of the cholesterol distribution are compared In the top 30 per cent of the cholesterol distribution 46 out of 247 men are overweight compared with 23

TABLE C5 15

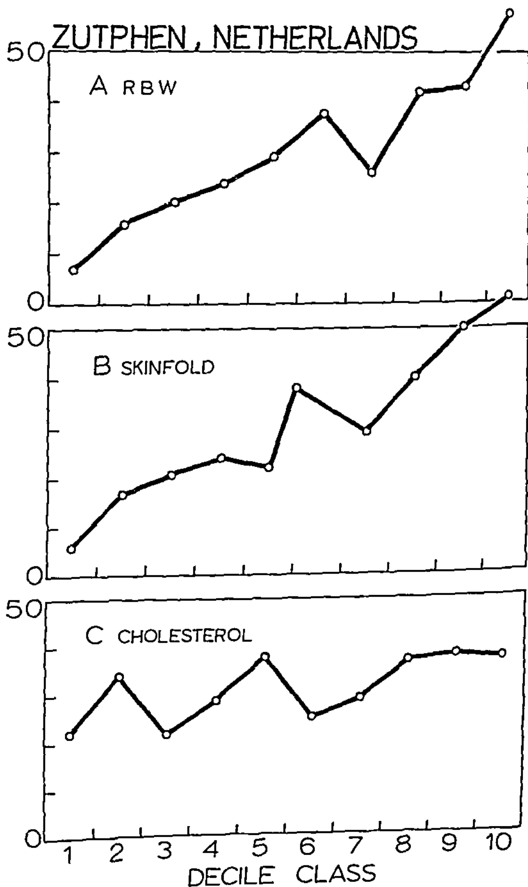
revalence of diastolic hypertension (95 or more 100 or more mm Hg fifth phase) mong men classed by age Percentage of men at Zutphen who are hypertensive ompared with the average for all 18 samples of men

AMPLE	40 44		45-49		50-54		55 59	
	95 mm	100 mm	95 mm	100 mm	95 mm	100 mm	95 mm	100 mm
utphen	29 4	19 4	29 1	17 7	30 9	23 2	31 6	22 7
Mean 18 samples	13 6	7 9	15 6	8 9	20 9	13 5	21 5	13 8

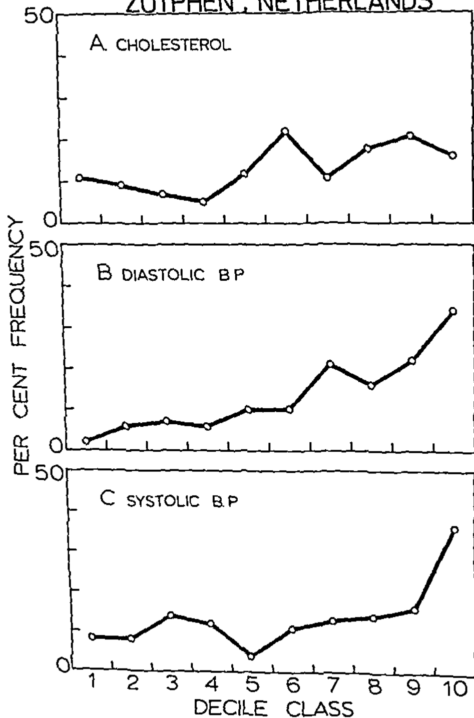
TABLE C5 16

Prevalence of overweight (110 or more and 120 or more per cent of "standard" average for height and age) Percentage of men at Zutphen classed by age who are overweight compared with the average for all 18 samples of men

SAMPLE	40 44		45 49		50-54		55-59	
	110%	120%	110%	120%	110%	120%	110%	120%
Zutphen	14 9	3 3	13 5	3 8	13 7	1 7	11 6	2 7
Mean 18 samples	20 9	8 4	19 4	6 9	18 1	6 7	16 8	7 3



ZUTPHEN, NETHERLANDS
A RBW
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
50
0
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS


ZUTPHEN, NETHERLANDS
A. CHOLESTEROL
B DIASTOLIC B.P
C SYSTOLIC B.P
PER CENT FREQUENCY
50
0
50
0
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

out of 250 men in the bottom 30 per cent of the distribution, chi-square = 8 60 and p = about 0 005

Summary

In the commercial town of Zutphen in the eastern part of the Netherlands a statistical sample of four out of nine *men aged 40—59 was drawn and 84 3* per cent of these men (N = 917) were examined Only 11 3 per cent of these *men were engaged in heavy physical* activity, 24 1 per cent were sedentary or did only light work

*In general compared with other sam*ples in these studies the men of Zutphen were somewhat above the average in relative body weight, Σ skinfolds blood pressure and serum cholesterol Most of them were cigarette smokers but only 10 7 per cent smoked 20 or more cigarettes daily The non-smokers tended to be more often overweight and obese and to have higher blood pressures than the smokers Electrocardiographic abnormalities in rest and after exercise were not very common but tended to be somewhat more prevalent than in the rural populations studied in Italy Greece Yugoslavia and Japan

Hypertension was common by any criteria and was especially prevalent among men in the upper part of the distributions of relative weight Σ skinfolds and serum cholesterol concentration *Similarly* overweight was unduly common among men in the upper part of the distributions of blood pressure and *serum cholesterol*

High values for relative weight Σ skinfolds blood pressure and serum *cholesterol* were *more common among* sedentary than among more active men and among men in the higher socio eco*nomic class than in the lower class*

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C6 RURAL POPULATIONS IN CRETE AND CORFU, GREECE

by Christ Aravanis A S Dontas D Lekos and Ancel Keys

Introduction

An early decision in the plans for the present series of studies was to include at least one sample of men whose habitual diet is high in fat but low in saturated fatty acids Populations eating large amounts of olives and olive oil would meet these specifications and among many such populations at the eastern end of the Mediterranean Sea the island of Crete is a classical example In the vicinity of Iraklion (Herakhon the ancient Candia) the olive tree has been a major source of food for at least five thousand years great pottery jars and vats for the storage of olive oil are numerous in the ruins of the palace of Minos and other remnants of the Minoan civilization

Crete also had the advantage of being the subject of an intensive study shortly after World War II sponsored by the Rockefeller Foundation which provided much information about health conditions diet etc (Albaugh 1953) That study documented the fact of the continued prominence of olives and especially olive oil and small consumption of meats and dairy products in a simple but reasonably abundant diet Cardiovascular diseases appeared to be relatively uncommon from the rather superficial information on morbidity and mortality collected by the Rockefeller group

The later decision to include a study on the island of Corfu was based on information that the diet there is similar to that in Crete but that the attitudes and social psychology there are much more European in contrast with the Cretans whose psychology is more Oriental Our preliminary survey of middle aged men in eleven villages in Crete in 1957 had shown a remarkable rarity of coronary heart disease and the question was raised as to whether in part this was related to the fatalistic philosophy and preservation of the old unhurried ways characteristic of rural Crete In short comparison of Crete and Corfu offered the prospect of comparing two populations of Greek farmers eating much the same diet and practicing the same kind of handlabor agriculture but perhaps differing in tension

Crete

The mountainous island of Crete with an area of 3 600 square kilometers and a population today of 550 000 is a land of small farmers with a very long

history The island gave birth to the Minoan Civilization some 5,000 years ago but beginning with the incursion of *the Dorians early in Greek history from* what now is Greece proper it has seldom been free from invasions and protracted foreign rule—notably by the Romans Venetians and Turks Finally, *in 1913* Crete again became an integral part of Greece Though there is no separatist sentiment, even today the population *tends to consider itself Cretan* as well as Greek Hundreds of years of Turkish rule left its mark so that the culture of Crete is relatively less Western and modern than that of other parts of Greece

The climate is warm-temperate rain is rather scanty and the land is dry a good deal of the year in many parts of the island Basically the only industry is agriculture and this is concentrated *on a few crops chiefly table grapes,* olives and olive oil white currants nuts and pulses Table grapes for export are a major cash crop in the study area The olive has been of key importance in the diet since Minoan times and there is reason to believe that the local diet has changed little for many centuries

The area under study on Crete consists of a series of villages inhabited by small farmers centered at Kastelli, about 30 km east and inland from the port city of Iraklion In modern times many young men tend to leave these villages seeking opportunity in Iraklion Athens or overseas they seldom return Aside from such migration and a little *movement* between villages the population of these villages is very stable poor in money and many amenities of modern life but *relatively content* As in the rest of Crete the Greek Orthodox religion prevails

Corfu

The verdant island of *Corfu* with an area of 589 square kilometers lies just *off the Greek mainland in the Ionian* Sea Homer, in the Odyssey called it Pheakon Corfu was a part of Greece as early as the 8th century B C but was dominated by the Romans from 300 B C to 400 A D, then by Byzantium until 1200 by Venice from 1386 to 1797 by France and Russia from 1797 to 1814 and by England from 1815 to 1864 when it finally came back to Greek rule

The climate is warm-temperate and humid, with a long rainy season contrasting with the more arid climate of much of Greece Except for some trade as a tourist center (and winter home of royal families in the 19th and early 20th centuries), the industry of the island is purely agricultural the main produce being olives and olive oil, grapes pulses and fruits

Sociologically Corfu is much more *"European" than is Crete though* both are wholly Greek and the Greek Orthodox Church is dominant Among rural areas in Greece *Crete is perhaps the* least Western in outlook and manner while Corfu is one of the most occidental and European

The area under study on Corfu comprises a series of farming villages in the northeastern part of the island As elsewhere in Greek villages there has been some outward migration of young men but otherwise the population is stable

As indicated in Section A a survey was made in 1957 on the island of Crete in which the attempt was to examine substantially all of the men then aged 45—65 in a selected series of villages The protocol and methods were similar to those employed in the study *in the fall of 1960* here *reported* For the 1960 study the general area was the same but the age range was changed *to cover men aged 40—59 inclusive* at the time of the examinations and for the sake of efficiency the geographical *boundaries were changed and reduced* so as to concentrate on six villages in-

stead of covering twelve as in 1957 Accordingly a considerable number of men examined in 1957 were re examined in 1960 in Crete

Both in Crete and Corfu the initial rosters compiled from official local records proved to contain many inaccuracies — they listed some men who had long since moved to other parts of Greece or had emigrated abroad a few who had died A few men who had permanently moved into the study villages were not in the offical lists of our villages but were considered to be properly included in our study population Finally some clerical errors in name or date of birth were corrected to provide the final roster

In both areas the cooperation was excellent and the result was that the examinations covered 686 out of 703 men in the roster in Crete (97 6 per cent) and 529 out of 555 men in the roster in Corfu (95.3 per cent) The data reported here cover slightly smaller numbers because some items of examination were inadvertently missed in occasional men and some blood samples were spoiled in the analysis Further when the statistical analysis was made check of birth dates showed that a few men were out of the age range at the actual time of their examinations and their data are not included here

Age, Physical Activity and Occupation

Table C6 1 gives the classifications of the men of Crete and Corfu by age and habitual physical activity In both areas there is a relative shortage of men aged 40—44 and in Corfu this shortage is also marked for men aged 45—49 Roughly there is a relative shortage of something like 60 men in the age class 40—44 in Crete i e over a fourth of that cohort in Corfu about the same proportion of men aged 40—49 who might be expected to be in the roster are no longer there

In large part this age structure must reflect losses in World War II and emigration thereafter The men aged 40—44 in 1960 and 1961 were those called first to defend Greece from the Italian and then from the German invasions at the start of these aggressions they were aged 19—23 (Corfu) or 20—24 (Crete) At the end of the war the survivors of those cohorts were aged 24—28 (Crete) or 25—29 (Corfu) During the war few of these young men had any possibility of marrying and establishing their own households in their native villages many of them had seen something outside of those villages they were no longer rooted in the local soil and were prone to seek opportunity in the cities or to emigrate

In Crete over 60 per cent of the men were habitually engaged in heavy physical work and less than 7 per cent were sedentary or did only light work Corfu stands in sharp contrast with less than a third of the men in Class 3 activity and an equal number in Class 1 The principal reason for this difference is the fact that the villages in the Corfu study are in close proximity to the port city of Corfu with many tourist establishments and holiday homes while the Crete villages are much more isolated

Table C6 2 shows the occupational distribution of the subjects in Crete and Corfu Three-fourths of the Cretans and over half of the men of Corfu are farmers More men are engaged in business and clerical work in the Corfu villages than in Crete but even in Corfu less than 9 per cent of the men are so occupied

Distribution of Measured Variables

Table C6.3 gives the median values of the men classed by age for relative body weight the sum of the *skinfolds*

TABLE C6 1

Men of Crete (1960) and Corfu (1961) classed by age (at time of examination) and habitual physical activity (1 = sedentary and light, 2 = moderate 3 = very active)

AGE	CRETE TOTAL MEN	CRETE % in ACTIVITY 1	2	3	CORFU TOTAL MEN	CORFU % in ACTIVITY 1	2	3
40-44	160	9 4	26 3	64 3	120	34 2	32 5	33 3
45-49	202	5 4	33 7	60 9	114	25 4	43 0	31 6
50-54	175	7 4	33 0	59 6	169	32 0	34 9	33 1
55-59	148	5 4	30 4	64 2	126	34 1	39 7	26 2
All Ages	685	6 9	31 0	62 1	529	31 6	37 2	31 2

TABLE C6 2

Men of Crete (1960) and Corfu (1961) classed by occupation

OCCUPATION	CODE	CRETE %	CORFU %	OCCUPATION	CODE	CRETE %	CORFU %
Professional	1-10	3 8	2 3	Metal work	62-65	1 7	2 1
Business etc	11-15	1 3	6 3	Agriculture	66-69 71-75	74 7	54 7
Foremen	16-22	0	1 1	Fishermen	70	0	2 4
Clerical	23-26	1 3	2 4	Factory work	78-80	0 6	1 1
Protection	27-30	1 2	1 4	Services	81-87	0 3	1 5
Food Handlers	*31-39*	*4 7*	*3 0*	*General labor*	*88 89*	*0 3*	*2 3*
Skilled light craft	40-44	2 2	2 0	Miscellaneous	90 94	1 3	1 9
Transportation	45-53	2 0	4 6	Not working	95-98	1 9	3 9
Building trades	54-61	2 6	6 9				

TABLE C6 3

Medians for the men of Crete and Corfu classed by age and those values expressed as percentage of the average of the medians for all 18 samples of men

ITEM	CRETE 40-44	CRETE 45-49	CRETE 50-54	CRETE 55-59	CORFU 40-44	CORFU 45-49	CORFU 50-54	CORFU 55-59
Height cm	166	166	166	165	167	166	166	164
" % of average	97 8	98 2	98 6	98 4	98 3	98 2	98 6	97 8
Relative Weight	94	91	92	88	94	93	92	90
" % of average	95 8	94 6	96 6	93 5	95 8	96 7	96 6	95 6
Σ Skinfolds mm	14	14	15	14	16	15	14	14
" % of average	66 0	68 6	72 5	70 4	75 5	73 5	67 6	70 4
Systolic B P mm	131	132	135	138	130	130	134	135
" % of average	100 0	99 2	98 5	98 2	99 2	97 7	97 8	96 0
Diastolic B P mm	80	80	81	83	81	80	81	81
" % of average	98 8	98 3	97 1	98 5	100 0	98 3	97 1	96 1
Serum Chol mg %	198	199	210	208	193	203	202	194
" % of average	95 9	96 0	100 5	100 7	93 5	97 9	96 7	93 9

blood pressure and serum cholesterol this table also shows these values expressed as percentages of the average medians for the men in all 18 samples in this cooperative study The cumulative frequency distributions of these variables are shown in Figures C6 1 C6 2 As elsewhere height is normally distributed and the skinfold thickness departs most notably from a normal distribution Details of the distributions are given in the Appendix

On the average the men of Crete and Corfu are almost identical in height and are similar in relative body weight and body fatness (sum of skinfolds) though the men of Crete tend to be a trifle thinner and less heavy than the Corfu men Compared with the average of all 18 samples these Greeks are somewhat short relatively underweight and decidedly thin If allowance is made for the true skin included in the skinfold measurement the average thickness of the subcutaneous fat over the triceps muscle and over the tip of the scapula is barely 5 mm the corresponding value for the average of the men in all samples is over 7 mm i e almost half again as much subcutaneous fat

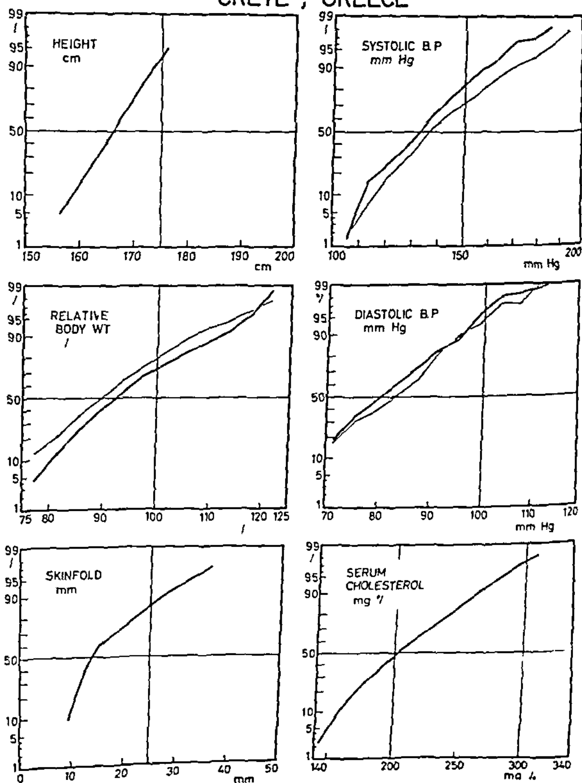
The men of Crete and Corfu do not differ importantly in arterial blood pressure and both in systole and diastole their blood pressure tends to be very slightly less than the average for all the men in this cooperative study In regard to serum cholesterol concentration there *is* a significant tendency for values to be lower in Corfu than in Crete but the difference is trifling only 6 mg per 100 ml in the middle of the distribution The median cholesterol values of these Greeks are about 3 per cent less than the average of *all 18 samples of* men

Age trends of these variables are not large over the ages 40—59 in these men For skinfold thickness and serum cholesterol age trends are small and inconsistent so all ages 40—59 were grouped for the cumulative frequency distributions shown in Figures C6 1 C6 2 In Crete the cholesterol median is 10 5 mg per 100 ml higher at ages 50—59 than at ages 40—49 but the difference is statistically not significant (chi-square = 2 64) As expected systolic blood pressure tends to rise with age but the average yearly increment is only 0 5 mm Hg in Crete and 0.3 in Corfu Diastolic blood pressure shows even less age trend more in Corfu and only an average rise of 0 2 mm per year in Crete

Activity and Socio Economic Status

In Crete and Corfu alike the frequency of relatively high values for the measured variables tended to be related to the habitual physical activity and to the socio-economic status of the men For both areas combined 17 1 per cent of all men were sedentary or engaged only in light activity (Class 1) while 48 8 per cent did heavy physical work (Class 3) If physical activity were unrelated to the measured variables the expectation would be that similar percentages of all men with high relative weight Σ skinfolds blood pressure and serum cholesterol would be found in these activity classes

If high values of the variables are taken to be the top 30 per cent of the distributions the percentage of all men with such high values who were found in Activity Class 1 proved to be *not* 17 1 but 26 6 for relative body weight 29 3 for Σ skinfolds 21 8 *for systolic* blood pressure 23 1 *for diastolic* blood pressure and 22 9 *for serum cholesterol* Similarly in Activity Class 3 instead of the expected value of 48 8 per cent the finding was 34 1 for relative weight 29.3 for Σ skinfolds 39 8 for systolic B P 39 8 for diastolic B P and 39 0 for cholesterol In effect the excess of relatively overweight men was 55 6 per cent among men in Activity Class 1 and



CRETE , GREECE
HEIGHT
cm
99
95
90
50
10
5
1
150
160
170
180
190
200
cm
SYSTOLIC B.P
mm Hg
100
150
200
mm Hg
RELATIVE
BODY WT
75
80
90
100
110
120
125
DIASTOLIC B.P
mm Hg
70
80
90
100
110
120
mm Hg
SKINFOLD
mm
0
10
20
30
40
50
mm
SERUM
CHOLESTEROL
140
200
250
300
340

Figure C6 1

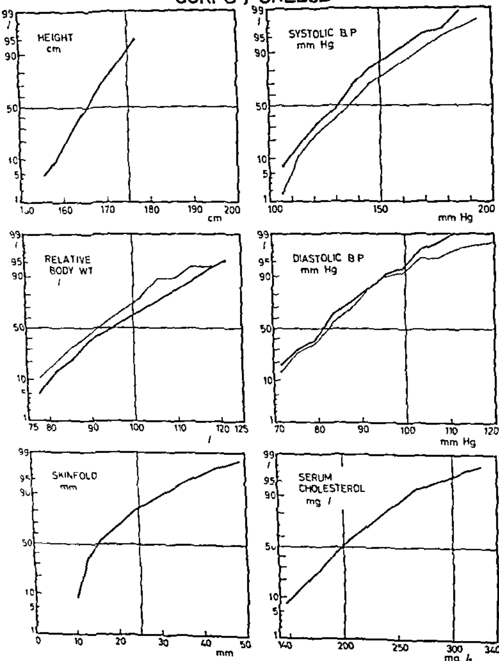
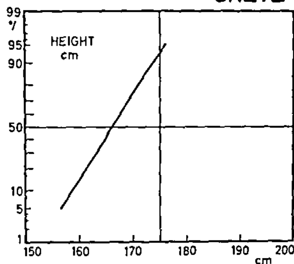
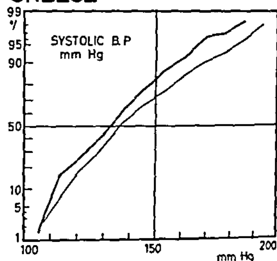
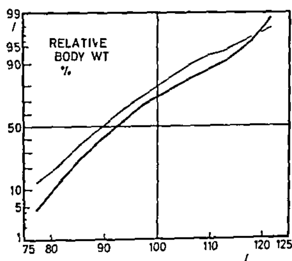

CORFU , GREECE
HEIGHT
cm
SYSTOLIC B P
mm Hg
RELATIVE
BODY WT
DIASTOLIC B P
mm Hg
SKINFOLD
mm
SERUM
CHOLESTEROL
mg

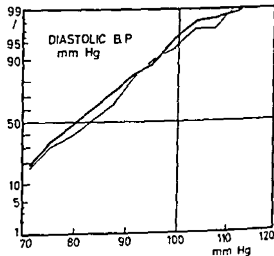
Figure C6 2

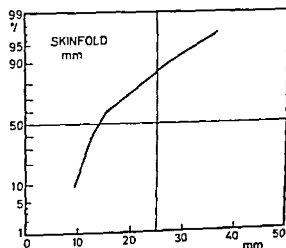
CRETE, GREECE











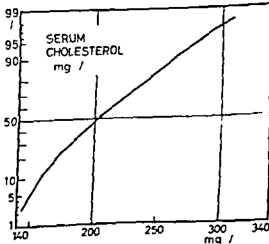


TABLE C6 4

Activity 1 vs Activity 2 Excess frequency of high values (deciles 8 10) of the variables observed among men of Activity 1 expressed as % of expectation from total numbers of men in Activities 1 plus 2 Also chi square values for the differences between observed and expected distributions

OCCUPATION	REL WT Excess	REL WT Chi²	Σ SKINFOLDS Excess	Σ SKINFOLDS Chi²	SYST B P Excess	SYST B P Chi²	DIAST B P Excess	DIAST B P Chi²	CHOLESTEROL Excess	CHOLESTEROL Chi²
Corfu										
1 94	22 1	7 17	28 6	1[illegible] 03	12 1	1 90	16 5	3 48	9 7	1 15
1 13	8 0	0 85	1 9	0	0 7	0	0 9	0	17 6	1 25
14 94	21 1	4 67	27 7	8 88	9 0	0 73	15 9	2 45	7 2	0 45
Crete										
1 94	75 7	15 40	74 7	18 53	19 4	0 61	54 4	6 60	49 3	5 21
1 13	23 2	4 56	15 6	2 11	23 1	0 51	2 0	0	28 2	1 42
14 94	45 2	1 46	71 4	9 21	25 0	0 33	83 3	5 68	61 3	3 01

TABLE C6 5

Activity 2 vs Activity 3 Occupations 14 94 only Excess frequency as in Table C6 4 of high values among men of Activity 2

SAMPLE	REL WT Excess	REL WT Chi²	Σ SKINFOLDS Excess	Σ SKINFOLDS Chi²	SYST B P Excess	SYST B P Chi²	DIAST B P Excess	DIAST B P Chi²	CHOLESTEROL Excess	CHOLESTEROL Chi²
Corfu	21 6	6 24	29 7	11 16	11 3	2 05	8 1	0 91	13 3	2 97
Crete	30 3	8 96	47 1	21 40	27 5	8 06	18 4	3 27	21 3	4 55

TABLE C6 6

Occupation 1 13 vs 14 94 Excess frequency as in Table C6 4 of high values among men in Occupations 1 13 expressed as % of expectation from total numbers of men in Occupations 1 13 + 14 94

ACTIVITY	REL WT Excess	REL WT Chi²	Σ SKINFOLDS Excess	Σ SKINFOLDS Chi²	SYST B P Excess	SYST B P Chi²	DIAST B P Excess	DIAST B P Chi²	CHOLESTEROL Excess	CHOLESTEROL Chi²
Corfu										
1 2	100 0	13 85	91 9	12 61	63 0	4 88	46 1	2 29	13 6	0 09
1	50 0	3 94	46 8	4 12	46 1	2 68	23 6	0 53	22 0	0 37
2	263 6	7 35	17[illegible] 7	2 50	66 7	0 11	81 8	0 20	0	0 59
Crete										
1 2	6 5	14 17	66 7	14 20	8 4	0 05	36 4	2 62	10 2	0 09
1	24 1	4 36	11 1	1 02	4 8	0	9 9	0 16	5 7	0
	40 0	0 75	56 2	2 71	31 0	0 49	45 5	1 20	21 6	0 11

Probabilities p associated with chi square values 2 71 p - 0 10 3 84 p - 0 05 5 41 p 0 02 6 64 p 0 01 10 83 p 0 001

in this activity class excesses for relative obesity were 71 3 per cent for systolic blood pressure 27 5 per cent for diastolic blood pressure 35 0 per cent and for serum cholesterol 28 7 per cent

The corresponding analysis for socio-economic status is hampered by the fact that very few men in these populations can be safely classed as being in a higher socio-economic class than the rest of the men Only 61 men in Corfu and Crete were in Occupations 1—13, so this upper socio-economic class represents only 4 9 per cent of the samples But in this class are found 11 6 per cent of all "overweight" men (deciles 8—10 in relative body weight) 12 4 per cent of "obese" men (deciles 8—10 in Σ skinfolds), 7.3 and 8 3 per cent, respectively, of all men with higher systolic and diastolic blood pressures (deciles 8—10) and 6 5 per cent of all men with higher cholesterol values (deciles 8—10)

Physical activity and socio-economic status are so closely correlated (inversely) in this material that they cannot be sharply separated in further analysis Tables C6 4 C6 5 and C6 6 summarize attempts in this direction Within the higher socio-economic class (Occupations 1—13) only Activity Classes 1 and 2 can be compared because Class 3 is not represented Table C6 4 shows that within this higher socio-economic class the only significant difference between Activity Classes 1 and 2 is in relative weight on the island of Crete Failure to find other differences may reflect the small number of men involved as well as the relatively small difference in physical activity concerned

Occupation Classes 14—94 include large numbers of men in both Activity Classes 2 and 3 and a substantial number (N = 169) in Class 1 But it is a gross over-simplification to consider all men in Occupations 14—94 to be uniform in socio-economic status So the differences, within Occupations 14—94 between men in the three Activity Classes indicated in Tables C6 4 and C6 5 cannot all be ascribed to physical activity

The comparisons between men in different Occupation Classes shown in Table C6 6 on the other hand give minimal estimates of differences related to socio-economic status The net result of consideration of all these data is to conclude that both physical activity and socio-economic status are important influences but their relative effects cannot be accurately estimated

Smoking Habits

For centuries Greece has been a large producer of tobacco almost all being of the "Turkish" type and the majority of men everywhere are regular cigarette smokers In Crete the water pipe or hookah is occasionally seen but this old Turkish custom of smoking has almost entirely disappeared The distribution of smoking habits by age is given in Table C6 7

Almost a fourth of these Greeks never smoked cigarettes and at the time of the examinations 42 8 per cent of the Cretans and 36 5 per cent of the men of Corfu were non-smokers The smokers in Crete tended to smoke more heavily than the smokers of Corfu and this difference is statistically highly significant The difference between the percentages of heavy smokers (20 or more cigarettes daily) in Crete and Corfu has a chi-square value of 9 55 and p = less than 0 01

The relationships between smoking habits and other characteristics of the men of Crete and Corfu examined in detail in Section F below are summarized in Table C6 8 Here it may be noted that as elsewhere the non-smokers in these samples tend to be relatively heavier and fatter than the smokers

The moderate cigarette smokers (10 to 19 cigarettes daily) are least often overweight or obese

Focussing on the men above the median values for their age and residence among the non smokers in Crete 63 per cent were above the median relative body weight and 64 per cent were above the median value of the sum of the skinfolds The corresponding figures for Corfu for non-smokers are 66 per cent above the relative weight median 69 per cent above the median sum of skinfolds

The Greek non smokers showed similar but less remarkable trends to have higher blood pressure than the smokers For diastolic blood pressure for example 55 per cent of the non-smokers in Crete and 64 per cent of them in Corfu were above the median for their age and residence In both areas the non-smokers also tended to have somewhat higher values for serum cholesterol than the smokers but the trend is not statistically significant in either area when the distribution about the median is analyzed

Electrocardiographic Findings

Tables C6 9 C6 10 C6 11 and C6 12 summarize the electrocardiographic (ECG) findings classified according to the Minnesota Code in Crete and Corfu In both samples but particularly in Crete the ECG findings are notable for the relatively small number of abnormalities

In Crete only one man showed a definite pattern of previous infarction (Code I 1) in Corfu three men were in this category If both samples are combined the rate of prevalence of this finding is only 3.3 per thousand men A striking feature of the ECG records in Crete is the high frequency of sinus bradycardia more than 10 per cent of the men showing this peculiarity The prevalence of very slow heart rates in Crete accounts for the relatively high frequency of long P-R intervals the latter are not rate-corrected in this material

In Crete the post-exercise records increased the number of ischemic S-T depressions Thirteen men showed depressions (Code IV 1 2 or 3) in rest among men who showed no such abnormalities in rest twelve showed them in the post-exercise record The exercise test provoked no significant negative T waves (Code XII 1 2)

Significant ECG abnormalities were more numerous in Corfu than in Crete — three vs one Q wave (Code I 1) 22 S-T depressions (Code IV 1—3) vs 13 eleven negative T waves (Code V 1 2) vs four two atrial fibrillations vs none On the other hand left axis deviation (Code II 1) was more common in Crete than in Corfu In Corfu the exercise test added 14 cases of ischemic S-T depression and one case of negative T wave

Prevalence of Hypertension and Overweight

Over the age range 40—59 the prevalence of hypertension shows no consistent age trend in Corfu and in Crete the prevalence actually tends to fall from age 40—44 to 55—59 The data for diastolic hypertension are summarized in Table C6 13

In general, there is no significant difference between the two areas in the prevalence of hypertension Compared with the men in all 18 samples in these cooperative studies the prevalence of hypertension in Crete and Corfu is similar at ages 40—49 but at ages 50—59 these Greeks are less prone to hypertension and this difference is statistically highly significant At these older ages only about half as many of these Greeks

TABLE C6 7

Cigarette smoking habits of men of Crete and Corfu   Percentage of men who never smoked, who had stopped, who smoked 1-9, 10-19, 20 or more cigarettes daily at the time of their examination

SAMPLE	AGE	NEVER	QUIT	1-9	10-19	20 OR MORE
Crete	40-44	20 0	18 1	8 1	21 3	32 5
"	45-49	26 7	17 3	9 9	15 3	30 8
"	50-54	24 4	19 3	11 9	15 3	29 1
"	55-59	23 0	21 6	10 8	17 6	27 0
"	40-59	23 8	19 0	10 2	17 2	29 8
Corfu	*40-44*	*26 7*	*7 5*	*12 5*	*32 5*	*20 8*
"	45-49	27 1	13 2	20 2	19 3	20 2
"	50-54	21 3	12 4	11 2	33 2	21 9
"	55-59	24 6	14 3	11 1	26 2	23 8
"	40-59	24 6	11 9	13 4	28 4	21 7

TABLE C6 8

Smoking   Number of men in Greece below (LOW) and above (HIGH) the age specific medians, for age and area, of measured variables, classed according to smoking habits   *HEAVY = 20 or more, OTHER = 1-19 cigarettes daily*

VARIABLE	SAMPLE	NON-SMOKERS		HEAVY		OTHER	
		LOW	HIGH	LOW	HIGH	LOW	HIGH
Relative Weight	Crete	113	167	118	83	106	77
"	Corfu	66	126	75	40	123	98
Σ Skinfolds	Crete	105	188	129	75	109	79
"	Corfu	59	134	72	43	133	88
Systolic B P	Crete	131	157	115	88	92	95
"	Corfu	80	113	63	52	121	100
Diastolic B P	Crete	129	159	118	85	91	96
"	Corfu	70	113	68	4[illegible]	126	95
Serum Cholesterol	Crete	136	147	95	96	96	82
"	Corfu	89	99	61	54	110	108

TABLE C6 10

CRETE GREECE

FREQUENCY OF POST EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (1,6)	45-49 (200)	50 54 (174)	55 59 (146)
Exercise tests not made or incomplete	X 1 X 2	2 (12 7)	2 (9 9)	2 (11 4)	1 (6 8)
S T Depression post exercise (none at rest)	XI				
S T J 1 mm or more horiz or downward segment	1	0	2 (10 0)	1 (5 7)	0
S T J 0 5 1 mm horiz or downward segment	2	1 (6 4)	3 (15 0)	3 (17 2)	1 (6 8)
No S T J plus segment downward	3	0	0	1 (5 7)	0
S T J 1 mm or more upward segment	4	7 (44 9)	12 (60 0)	4 (23 0)	5 (34 2)
T Wave Negativity post exercise (none at rest)	XII				
5 mm or more	1	0	0	0	0
1 to 5 mm	2	0	0	0	0
0 + 1 mm	3	2 (12 8)	2 (10 0)	2 (11 5)	2 (13 7)
Arrhythmias post exercise (none at rest)	XV 1	1 (6 4)	2 (10 0)	3 (17 2)	2 (13 7)
Technically poor post exercise records	XI 8	6 (38 5)	7 (35 0)	11 (63 2)	6 (41 1)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

At Rest					
Large Q Waves	I 1	0	0	1 (5 7)	0
Lesser Q Waves with Negative T Waves	I 2 3 + V 1 2	0	0	0	0
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	1 (6 3)	2 (9 9)	1 (5 7)	1 (6 8)
S T Depression as sole anomaly	IV 1 4 only	0	1 (5 0)	3 (17 0)	0
High Amplitude R with S T Depression	III 1 + IV 1 4	2 (12 7)	0	0	0
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2 4	1 (6 3)	1 (5 0)	0	3 (20 4)
Arrhythmias	VIII 2 6	0	1 (5 0)	1 (5 7)	2 (13 6)
Po t ex rcise					
S T Depression as sole anomaly	XI 1-4 only	6 (38 5)	8 (40 0)	6 (34 5)	3 (20 5)
N gative T as sole anomaly	XII 1 3 only	1 (6 4)	1 (5 0)	1 (5 7)	1 (6 8)
Ventricular Conduction Defect as sole anomaly	XIV 1 2 4 only	0	0	0	0
Arrhythmias as sole anomaly	XV 1 only	1 (6 4)	0	1 (5 7)	2 (13 7)

TABLE C6 9

CRETE GREECE

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code		AGE GROUP (Number of Men) 40-44 (158)	45-49 (202)	50 54 (176)	55 59 (147)
Total with reportable ECG Items	I - IX		64 (405 1)	94 (465 3)	81 (460 2)	84 (571 4)
Q Waves	I	1	0	0	1 (5 7)	0
		2	1 (6 3)	0	1 (5 7)	0
		3	1 (6 3)	2 (9 9)	2 (11 4)	1 (6 8)
Axis Deviation	II					
Left		1	2 (12 7)	9 (44 6)	13 (73 9)	8 (54 4)
Right		2	0	0	0	0
High Amplitude R Waves	III					
Left type		1	11 (69 6)	6 (29 7)	7 (39 8)	11 (74 8)
Right type		2	0	0	0	0
S-T Depression (rest)	IV					
S-T - J 1 mm or more horiz or downward segment		1	0	0	2 (11 4)	0
S-T - J 0 5 - 1 mm horiz or downward segment		2	3 (19 0)	2 (9 9)	2 (11 4)	3 (20 4)
No S T-J plus segment downward		3	1 (6 3)	0	0	0
S T - J 1 mm or more upward segment		4	0	0	1 (5 7)	0
T Wave Negativity (rest)	V					
5 mm or more		1	0	0	0	0
- 1 mm to -5 mm		2	1 (6 3)	1 (5 0)	1 (5 7)	1 (6 8)
0 ± 1 mm		3	4 (25 3)	5 (24 8)	3 (17 0)	1 (6 8)
A-V Conduction Defect	VI					
Complete Block		1	0	0	0	0
Partial Block		2	0	0	0	0
P-R over 0 21 second		3	6 (38 0)	3 (14 9)	5 (28 4)	9 (61 2)
Accelerated Conduction		4	1 (6 3)	0	0	0
Ventricular Blocks	VII					
Left Bundle		1	0	0	0	0
Right Bundle		2	1 (6 3)	1 (5 0)	0	3 (20 4)
Incomplete Right Bundle		3	3 (19 0)	3 (14 9)	2 (11 4)	3 (20 4)
Intraventricular Block		4	0	0	0	0
Arrhythmias	VIII					
Premature Beats		1	1 (6 3)	3 (14 9)	3 (17 0)	1 (6 8)
Ventricular tachycardia		2	0	0	0	0
Atrial fibrillation flutter		3	0	0	0	0
Supra-vent tachycardia		4	0	0	0	1 (6 8)
Ventricular rhythm		5	0	0	0	0
A V nodal rhythm		6	0	1 (5 0)	1 (5 7)	1 (6 8)
Sinus tachycardia		7	3 (19 0)	2 (9 9)	3 (17 0)	1 (6 8)
Sinus bradycardia		8	14 (88 6)	27 (133 7)	19 (108 0)	19 (129 3)
Technically poor records	IX	6	0	0	1 (5 7)	0

TABLE C6 12

CORFU GRFECE

FREQUENCY OF POST FXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40 44 (119)	45 49 (112)	50 54 (164)	55 59 (118)
Exercise tests not made or	X 1				
incomplete	X 2	1 (8 3)	2 (17 5)	5 (29 6)	8 (63 5)
S T Depression post exercise (none at rest)	XI				
S T J 1 mm or more horiz or downward segment	1	0	0	2 (12 2)	1 (8 5)
S T J 0 5 1 mm horiz or downward segment	2	0	2 (17 9)	4 (24 4)	5 (42 4)
No S T J plus segment downward	3	0	0	0	0
S T J 1 mm or more upward segment	4	2 (16 8)	4 (35 7)	5 (30 5)	5 (42 4)
T Wave Negativity post exercise (none at rest)	XII				
5 mm or more	1	0	0	0	0
1 to 5 mm	2	0	0	1 (6 1)	0
0 + 1 mm	3	0	0	0	0
Arrhythmias post exercise	XV				
(none at rest)	1	2 (16 8)	1 (9 0)	0	1 (8 5)
Technically poor post exercise records	XI 8	3 (25 2)	3 (26 8)	11 (67 1)	7 (59 3)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

ECG FINDING	ECG Code	40 44	45 49	50 54	55 59
At Rest					
Large Q Waves	I 1	0	0	1 (5 9)	2 (15 9)
Lesser Q Waves	I 2 3 +				
with Negative T Waves	V 1 2	0	0	0	0
Deeply Negative T as sole	V 1				
anomaly	only	0	0	0	1 (7 9)
Other Negative T as sole	V 2 3				
anomaly	only	0	0	2 (11 8)	1 (7 9)
S T Depression as sole	IV 1 4				
anomaly	only	2 (16 7)	2 (17 5)	1 (5 9)	1 (7 9)
High Amplitude R	III 1 +				
with S T Depression	IV 1 4	1 (8 3)	2 (17 5)	0	2 (15 9)
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2 4	2 (16 7)	1 (8 8)	5 (29 6)	3 (23 8)
Arrhythmias	VIII 2 6	0	0	2 (11 8)	1 (7 9)
Post exercise					
S T Depr ssion as sole	XI 1 4				
anomaly	only	2 (16 8)	2 (17 9)	5 (30 5)	4 (33 9)
Negat ve T as sole	XII 1 3				
anomaly	only	0	0	0	0
V ntr cular Conduction D fect as	XIV 1 2 4				
sole anomaly	only	0	0	0	0
Arrhythmias	XV 1				
as sole anomaly	only	2 (16 8)	1 (8 9)	0	0

TABLE C6 11

CORFU GREECE

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code		AGE GROUP (Number of Men) 40-44 (120)	45-49 (114)	50-54 (169)	55 59 (126)
Total with reportable ECG Items	I - IX		24 (200 0)	30 (263 2)	44 (260 4)	36 (285 7)
Q Waves	I	1	0	0	1 (5 9)	2 (15 9)
		2	0	0	2 (11 8)	2 (15 9)
		3	2 (16 7)	3 (26 3)	4 (23 7)	1 (7 9)
Axis Deviation	II					
Left		1	1 (8 3)	0	4 (23 7)	5 (39 7)
Right		2	0	0	0	0
High Amplitude R Waves	III					
Left type		1	5 (41 7)	10 (87 7)	11 (65 0)	14 (111 1)
Right type		2	0	0	0	0
S-T Depression (rest)	IV					
S-T - J 1 mm or more, horiz or downward segment		1	0	1 (8 8)	3 (17 8)	3 (23 8)
S-T - J 0 5 - 1 mm , horiz or downward segment		2	4 (33 3)	3 (26 3)	4 (23 7)	1 (7 9)
No S-T-J plus segment downward		3	1 (8 3)	0	0	2 (15 9)
S-T - J 1 mm or more upward segment		4	0	0	0	0
T-Wave Negativity (rest)	V					
- 5 mm or more		1	0	0	0	2 (15 9)
- 1 mm to -5 mm		2	1 (8 3)	1 (8 8)	4 (23 7)	3 (23 8)
0 ± 1 mm		3	3 (25 0)	1 (8 8)	5 (29 6)	3 (23 8)
A-V Conduction Defect	VI					
Complete Block		1	0	0	0	0
Partial Block		2	1 (8 3)	0	1 (5 9)	0
P-R over 0 21 second		3	0	1 (8 8)	1 (5 9)	0
Accelerated Conduction		4	0	1 (8 8)	0	0
Ventricular Blocks	VII					
Left Bundle		1	1 (8 3)	0	1 (5 9)	0
Right Bundle		2	1 (8 3)	1 (8 8)	3 (17 8)	3 (23 8)
Incomplete Right Bundle		3	2 (16 7)	2 (17 5)	5 (29 6)	0
Intraventricular Block		4	0	0	1 (5 9)	0
Arrhythmias	VIII					
Premature Beats		1	3 (25 0)	2 (17 5)	3 (17 8)	1 (7 9)
Ventricular tachycardia		2	0	0	0	0
Atrial fibrillation flutter		3	0	0	2 (11 8)	0
Supra-vent tachycardia		4	0	0	0	1 (7 9)
Ventricular rhythm		5	0	0	0	0
A V nodal rhythm		6	0	0	0	0
Sinus tachycardia		7	4 (33 3)	3 (26 3)	2 (11 8)	1 (7 9)
Sinus bradycardia		8	1 (8 3)	1 (8 8)	2 (11 8)	1 (7 9)
Technically poor records	IX	8	1 (8 3)	1 (8 8)	1 (5 9)	0

are hypertensive as would be expected from the data on all 18 samples

The percentages of men who are overweight are given in Table C6 14 The men of Crete are less often grossly overweight (20 per cent or more above the standard" average for height and age) than the men of Corfu but in both areas the prevalence of overweight tends to be less than among all men in the 18 samples in these cooperative studies

Prevalence of Obesity and Hypercholesterolemia

Using the classification criteria developed in Section H below 13 per cent of the men of Crete have some degree of obesity but only 2 per cent were classed as Grade 1 (extremely obese) The corresponding figures for Corfu are 16 and 4 per cent

The prevalence of any degree of hypercholesterolemia using the criteria in Section H is 27 per cent in Crete 24 per cent in Corfu Grade 1 hypercholesterolemia characterized 7 per cent of the men in Crete 6 per cent of the men of Corfu Though these frequencies are substantial they are considerably lower than the average of all men in the 18 samples in the present studies

Hypertension versus Other Variables

If hypertension is judged to be present when the diastolic blood pressure is 95 mm or more 12 per cent of the men aged 40—59 were hypertensive in both Crete and Corfu The distributions of these hypertensive men into decile classes of relative body weight Σ skinfolds and serum cholesterol are shown in Figures C6.3 and C6 4 In both areas and for all three variables the prevalence of hypertension rises with increasing levels of these other variables most strikingly in the upper part of the distributions of relative body weight and Σ skinfolds for these two variables there is a marked trend to curvilinearity

More detailed inspection of Figures C6.3 and C6 4 and the data on which they are based shows that there is no significant tendency for the prevalence of hypertension to rise with either relative weight or Σ skinfolds over the first six or seven decile classes all of the significant relationship is contributed by the top three or four decile classes

The picture of hypertension distribution as related to serum cholesterol in this Greek material at first glance seems to be less dramatic than in the relative weight and Σ skinfold data but it is still highly significant Hypertension is more than twice as prevalent (2.2 times) among the men in the top 30 than in the bottom 30 per cent of the cholesterol distribution in Crete In Corfu the discrepancy is even more remarkable in the top 3 decile classes of cholesterol 29 out of 158 men were hypertensive in the bottom 3 deciles only 11 out of 158 men were so classed the relative frequency of hypertension in Corfu is 2 6 times higher in the upper than it is in the lower 30 per cent of the cholesterol distribution

Overweight versus Other Variables

Among men aged 40—59 the prevalence of overweight was 3 per cent in Crete and 6 per cent in Corfu if a relative body weight of 120 per cent of the U S averages in the Medico-Actuarial Investigations is taken as the criterion The difference between the areas though small is significant (chi-square = 6 40 p = less than 0 02)

The distributions of these overweight men into decile classes of serum cholesterol diastolic and systolic blood pressures are shown in Figures C6.5 and

TABLE C6 13

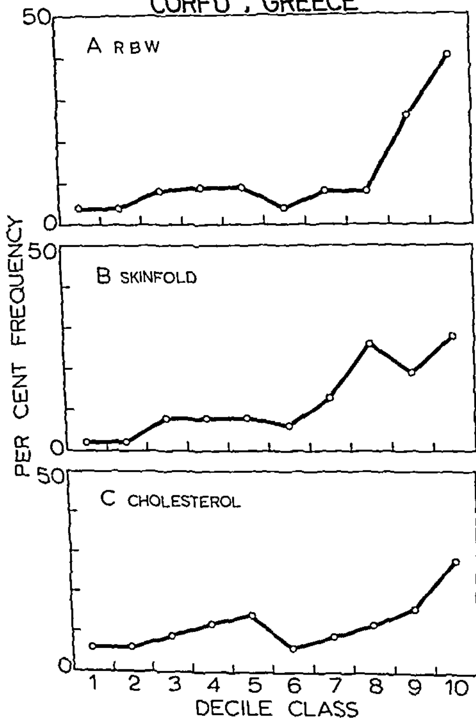
Prevalence of diastolic hypertension (95 or more, 100 or more mm Hg fifth phase) among men classed by age Percentage of men in Crete and Corfu who are hypertensive, compared with the average for all 18 samples of men

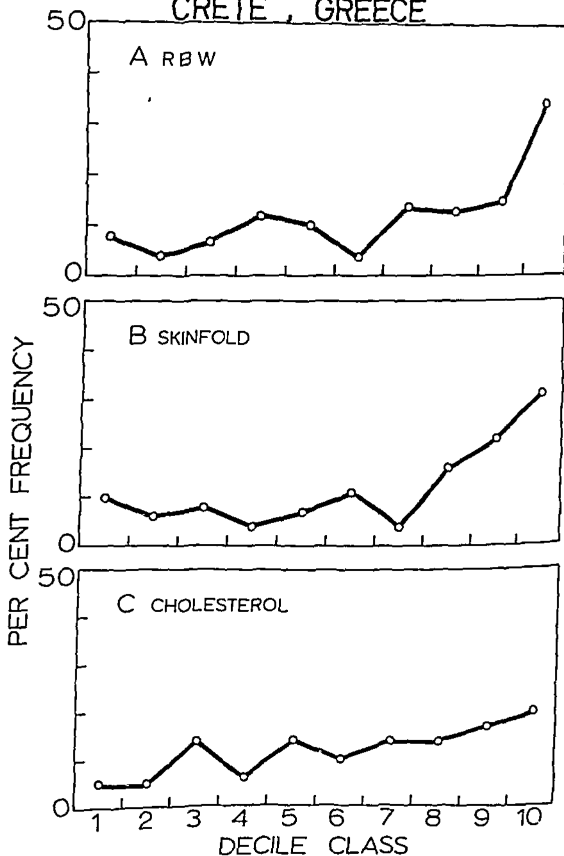
SAMPLE	40-44		45-49		50-54		55 59	
	95 mm	100 mm	95 mm	100 mm	95 mm	100 mm	95 mm	100 mm
Crete	13 9	5 7	13 4	5 0	11 0	6 4	9 6	5 5
Corfu	8 3	5 8	14 9	8 8	13 0	7 7	11 1	6 3
Mean, 18 samples	13 6	7 9	15 6	8 9	20 9	13 5	21 5	13 8

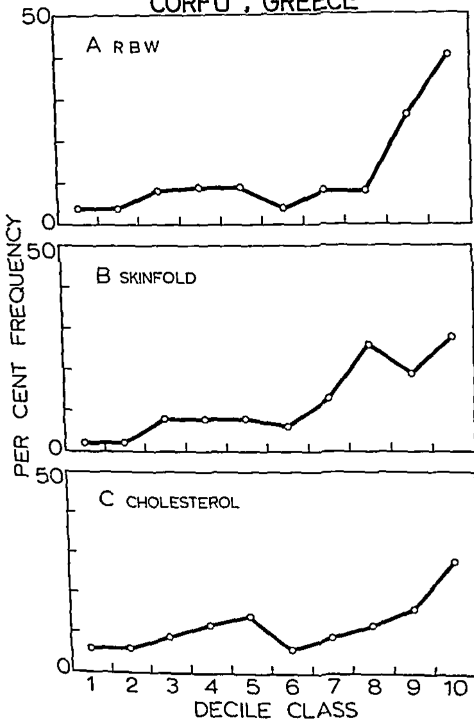
TABLE C6 14

Prevalence of overweight (110 or more and 120 or more per cent of standard average for height and age) Percentage of men in Crete and Corfu, classed by age who are overweight compared with the average for all 18 samples of men

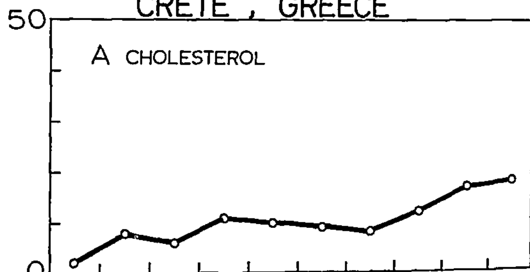
SAMPLE	40-44		45-49		50 54		55 59	
	110%	120%	110%	120%	110%	120%	110%	120%
Crete	13 1	2 5	10 9	3 0	10 8	4 5	4 1	1 4
Corfu	13 3	7 5	20 7	4 4	10 7	6 0	11 9	6 3
Mean, 18 samples	20 9	8 4	19 4	6 9	18 1	6 7	16 8	7 3

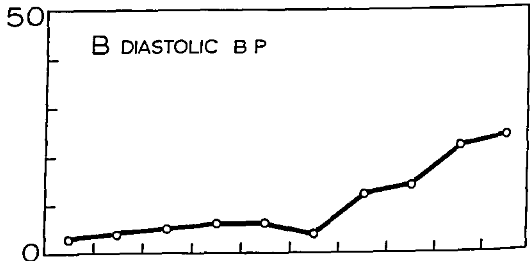

CORFU , GREECE
A RBW
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
50
0
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

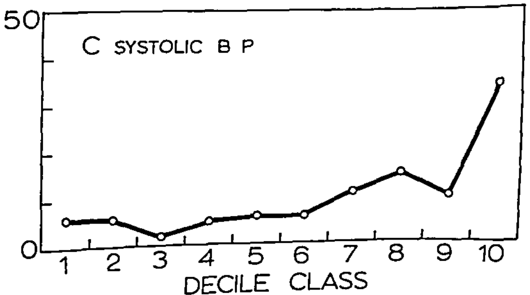

CRETE , GREECE
50
A RBW
0
50
B SKINFOLD
0
50
C CHOLESTEROL
0
PER CENT FREQUENCY
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

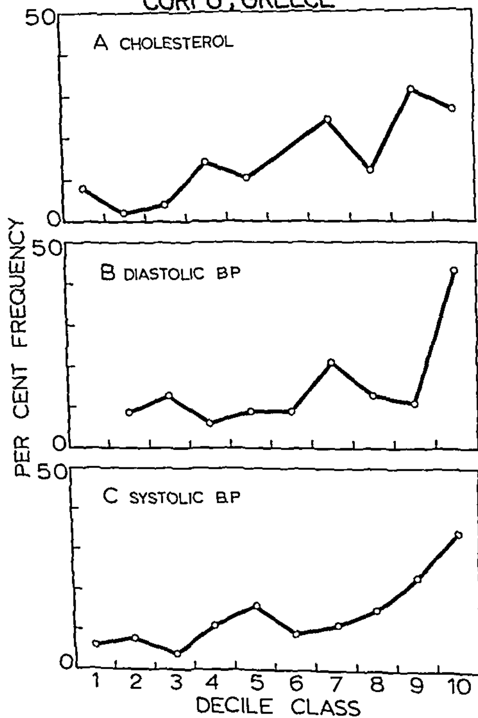

CORFU , GREECE
A RBW
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

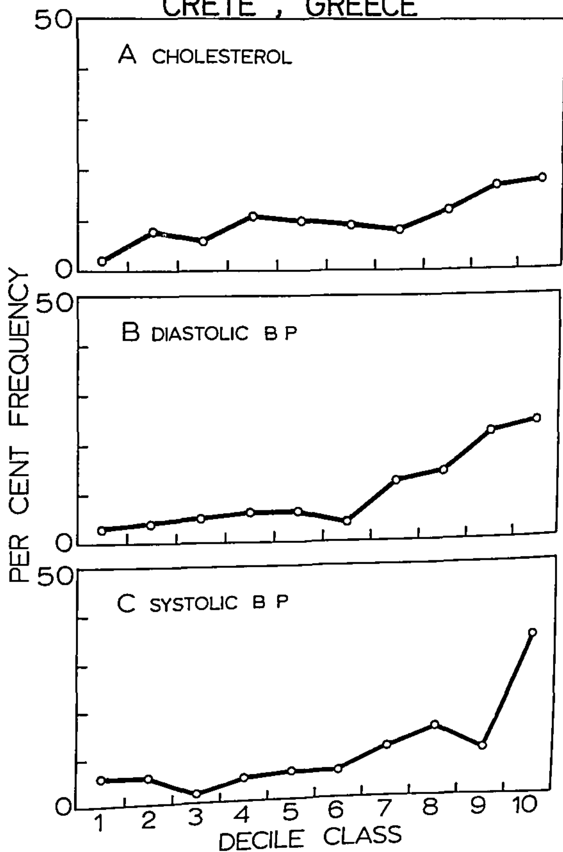
CRETE , GREECE



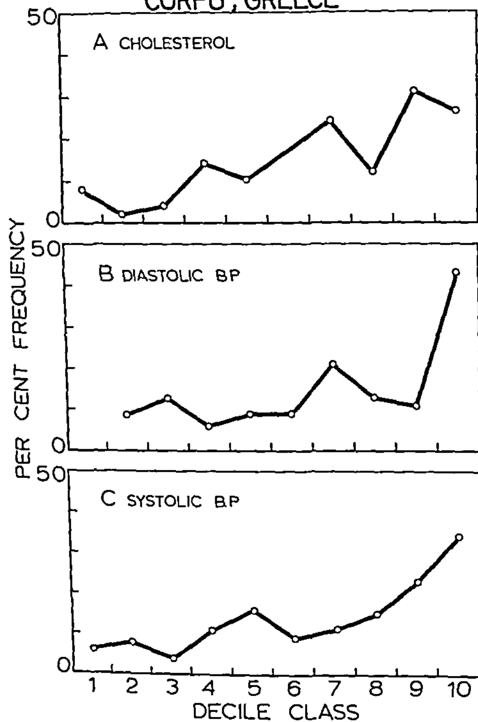





CORFU, GREECE
A CHOLESTEROL
B DIASTOLIC B.P
C SYSTOLIC B.P
PER CENT FREQUENCY
50
0
50
0
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS



CRETE , GREECE
A CHOLESTEROL
B DIASTOLIC B P
C SYSTOLIC B P
PER CENT FREQUENCY
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS



CORFU, GREECE
A CHOLESTEROL
B DIASTOLIC B.P
C SYSTOLIC B.P
PER CENT FREQUENCY
50
0
50
0
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

Figure C6.6

C6 6 In both areas the prevalence of overweight is markedly related to each of these other variables and in several cases at least the relationship appears to be curvilinear, with most of the trend being dependent on the top decile classes

Among 65 overweight men in Crete 31 were in the top and 10 in the bottom 30 per cent of the cholesterol distribution the corresponding numbers among 70 overweight men in Corfu are 36 and 7 men For diastolic blood pressure the discrepancies are similar in Crete 40 men were in the top and eight in the bottom 30 per cent of the diastolic blood pressure distribution in Corfu the corresponding figures are 36 *in the top 12 in the bottom*

Summary

In two rural areas of Greece, on the Islands of Crete and Corfu 96 6 per cent of all men aged 40—59 (N = 1215) were examined Over 60 per *cent of the men of Crete were engaged* in heavy physical work and only 6 9 per cent were sedentary or engaged in only light activity The corresponding percentages for Corfu were 31 2 per cent heavy activity *31 6* sedentary or only light work

In both areas the men tended to be decidedly thinner and somewhat lower in relative body weight than the average men in the other samples in these studies In both areas the men in the higher socio-economic classes or who were characterized by low physical activity *tended to be over-represented* in the upper ends of the distributions of relative body weight Σ skinfolds blood pressure and serum cholesterol

In both areas most of the men smoked cigarettes The *non-smokers* were *much more often relatively* overweight and fat than the smokers and also tended to have higher blood pressures and serum cholesterol values

Significant electrocardiographic abnormalities were uncommon in both areas and were especially rare in Crete Post-exercise records increased the number of abnormalities but the total *prevalence of indications of myocardial* ischemia was still low

Hypertension was less common in these Greek samples than the average for all samples in these studies and the prevalence was similar in Crete and Corfu In both areas hypertension prevalence rose sharply with increasing relative body weight and Σ skinfolds in *the upper part of the distributions* of these variables The prevalence of hypertension was also directly related to serum cholesterol level

Overweight was uncommon in these samples in Crete large degrees of overweight were especially rare The prevalence *of overweight tended to be* directly related to blood pressure and to serum cholesterol concentration

Acknowledgments

The research teams in Crete in 1960 and in *Corfu in 1961 included Drs* Christ Aravanis C Chlouverakis A S Dontas D Lekos A Papadopoulus E Staphylakis G Stamatoyannopoulos C Vasilikos and A Vlachopoulos *Valuable counsel as well as other aid was* provided by Prof George Michaelides and Dr D Papapanagiotou

*In Crete Dr G Hadgakis Health Commis*sioner for Heraklion and George Arnaoutakis were most helpful The work in Crete in 1960 *was made easier by the 1957 survey in which* help was provided by Drs Jacques Carlotti Flaminio Fidanza Martti J Karvonen Ancel *Keys Noboru Kimura and Paul Dudley White* and Mrs Margaret Haney Keys

In Corfu important aid was given by Dr *D Avramidis Health Commissioner*

C7 A FARMING AND A FISHING VILLAGE IN JAPAN — TANUSHIMARU AND USHIBUKA

by Noboru Kimura (Kurume)

Introduction

Because of much evidence that coronary heart disease is relatively uncommon in Japan though not among Americanized Japanese in the United States it was considered important to conduct systematic studies in that country It was planned to include several villages in Kyushu the southern island of Japan in the general program of cooperative work begun in 1957 at Nicotera in Italy but limitation of funds prevented the use of international teams and other arrangements used elsewhere to guarantee complete comparability However local efforts enabled similar surveys to be carried out in the spring of 1958 in a typical farming village Tanushimaru and in the summer of 1960 in a fishing village Ushibuka These villages afford contrasts both in the type of occupation and in the diet

Tanushimaru

This farming village in the northern part of Kyushu is entirely devoted to highly productive small scale farming of rice wheat fruits vegetables and arboriculture the produce being sold in the nearby markets of the city of Fukuoka and the town of Kurume Though the general population is rather poor and there is a high degree of socio-economic homogeneity those farmers who most intensively cultivate every meter of land as tree nurseries are relatively wealthy The climate is humid and warm-temperate but snow falls occasionally in winter The population tends to be stable in residence though as elsewhere in rural areas migration of young people to the cities is substantial

Ushibuka

Ushibuka is a fishing village on a small island offshore from Ariake Bay of Kyushu Most of the men are engaged in the heavy work of fishing in small boats which go out daily or for several days at a time In bad weather work is concentrated on building and repairing boats and nets Some farming serves purely local needs and there is no other industry The produce of the sea together with rice and vegetables dominates the diet large amounts of fish are eaten daily The population is rather isolated because of the island location and tends to exhibit the insular character of people in homogeneous settlements in remote places Ushibuka

C6 6 In both areas the prevalence of overweight is markedly related to each of these other variables and in several cases at least the relationship appears to be curvilinear, with most of the trend being dependent on the top decile classes

Among 65 overweight men in Crete 31 were in the top and 10 in the bottom 30 per cent of the cholesterol distribution the corresponding numbers among 70 overweight men in Corfu are 36 and 7 men For diastolic blood pressure the discrepancies are similar in Crete 40 men were in the top and eight in the bottom 30 per cent of the diastolic blood pressure distribution, in Corfu the corresponding figures are 36 in the top 12 in the bottom

Summary

In two rural areas of Greece on the Islands of Crete and Corfu 96 6 per cent of all men aged 40—59 (N = 1215) were examined Over 60 per cent of the men of Crete were engaged in heavy physical work and only 6 9 per cent were sedentary or engaged in only light activity The corresponding percentages for Corfu were 31 2 per cent heavy activity 31 6 sedentary or only light work

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In both areas most of the men smoked cigarettes The non-smokers were much more often relatively overweight and fat than the smokers and also tended to have higher blood pressures and serum cholesterol values

Significant electrocardiographic abnormalities were uncommon in both areas and were especially rare in Crete Post-exercise records increased the number of abnormalities but the total prevalence of indications of myocardial ischemia was still low

Hypertension was less common in these Greek samples than the average for all samples in these studies and the prevalence was similar in Crete and Corfu In both areas hypertension prevalence rose sharply with increasing relative body weight and Σ skinfolds in the upper part of the distributions of these variables The prevalence of hypertension was also directly related to serum cholesterol level

Overweight was uncommon in these samples in Crete large degrees of overweight were especially rare The prevalence of overweight tended to be directly related to blood pressure and to serum cholesterol concentration

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In Corfu important aid was given by Dr D Avramidis Health Commissioner

TABLE C7 1

Median values for Japanese men classed by age and these values expressed as percentage of the average of the medians for all 18 samples of men

SAMPLE and VARIABLE	MEDIAN VALUES 40-44	45-49	50-54	55-59	MEDIAN as % of AVERAGE 40-44	45 49	50 54	55 59
TANUSHIMARU								
(no of men)	(112)	(117)	(137)	(143)	(112)	(117)	(137)	(143)
Height, cm	162	161	159	160	95 4	95 2	94 5	95 4
Relative wt	89	86	84	84	90 7	89 4	88 2	89 3
Σ Skinfolds mm	15	15	14	15	70 8	73 5	67 6	75 4
Systolic B P mm Hg	120	128	132	138	91 6	96 2	95 7	98 2
Diastolic	68	70	72	78	84 0	86 0	86 3	92 5
Serum Cholesterol mg %	167	165	178	168	80 9	79 6	85 2	81 3
USHIBUKA								
(no of men)	(115)	(128)	(139)	(118)	(115)	(128)	(139)	(118)
Height cm	160	160	158	159	94 2	94 6	93 9	94 8
Relative wt	91	89	87	84	92 8	92 5	91 4	89 3
Σ Skinfolds mm	--	--	--	--	--	-	-	--
Systolic B P mm Hg	126	128	135	140	96 2	96 2	98 5	99 6
Diastolic	75	76	80	80	92 6	93 4	95 9	94 9
Serum Cholesterol mg %	142	143	137	144	68 8	69 0	65 6	69 7

TABLE C7 2

Cigarette smoking habits of men classed by age in Tanushimaru and Ushibuka Percentage of men who had never smoked men who had quit smoking and heavy smokers (20 or more cigarettes daily)

AGE	TANUSHIMARU Never	Quit	Heavy	USHIBUKA Never	Quit	Heavy
40 44	15 6	12 8	40 4	15 8	8 8	42 9
45 49	14 8	12 2	49 5	10 9	4 7	49 6
50 54	13 8	13 8	44 7	13 1	8 8	35 7
55 59	20 1	13 7	39 6	.0 3	6 8	31 2
40 59	16 2	13 2	43 4	14 9	7 2	37 7

TABLE C7 3

umber me be o (LO) and above (HI) age specific medians for all Japanese Tanushimaru l ft Ushibu a rigt hand Heavy 20 or more Other 1 19 cigarettees per day

	Non Smoker LO	HI	Heavy LO	HI	Other LO	HI	Non Smoker LO	HI	Heavy LO	HI	Other LO	HI
R l Wt		83	108	106	64	64	38	62	84	92	106	73
Σ S mm		83	108	106	71	61						
S 1 B P		75	100	164	86	66	38	72	99	8/	110	89
D 1 B P		8.	10.	11.	73	61	.3	33	92	93	112	87
S c		-	115	94	53	4	5	52	95	91	16	103

is seven hours by boat from the big city of Fukuoka The climate is warm-temperate similar to that of Tanushimaru but less cold in winter and generally less humid

Sample Coverage

Every Japanese adult must have an identification card and good local registries are maintained of births, deaths residents and voters so establishment of a reliable roster of all men aged 40—59 in a given locality is easy Some clerical errors in age and name are readily corrected by examination of identity cards In the villages excellent cooperation in medical surveys was obtained in exploratory studies in 1956 (Keys et al, 1958 a) and this experience was repeated in the studies reported here

All men aged 40—59 in the prescribed areas were invited for the examinations The extraordinary response of 99 6 per cent at Ushibuka and 100 per cent at Tanushimaru was obtained However, some errors in age were discovered at the time of the examinations and a considerable number of out-of-age volunteers also showed up Only data on men 40—59 at the time of examination are reported here (509 at Tanushimaru 500 at Ushibuka)

The age distributions of the men in these Japanese villages reflect the losses of younger men during World War II In both Tanushimaru and Ushibuka the age class 40—44 contained the fewest men in any of the 5-year age classes studied (22 1 per cent in Tanushimaru 22 9 in Ushibuka), the largest representation in both villages was in the age class 50—54 (26 4 per cent in Tanushimaru 27 6 in Ushibuka)

Distribution of Six Measured Variables

Table C7 1 gives the median values of the Japanese men classed by age for relative body weight (as percentage of the "standard" averages for given height and age tabulated in the Appendix), the sum of the skinfolds (over the triceps muscle and the tip of the scapula) systolic and diastolic (5th phase) blood pressure and serum cholesterol concentration Figures C7 1 and C7 2 show the cumulative frequency distributions (probability scale) of these variables Full details of the distributions are given in the Appendix

The farmers at Tanushimaru tend to be nearly 2 cm taller than the fishermen at Ushibuka and in both samples the men are shorter by about 8 to 9 cm on the average than the average of all men in the 18 samples in the present study Except at ages 55—59 where the men in the two villages are the same the relative body weight of the fishermen of Ushibuka is slightly greater than that of the farmers in Tanushimaru In both areas the men tend to be much lighter for their height and age than the average for all 18 samples

Body fatness was not measured at Ushibuka but the men at Tanushimaru tended to be very lean and this did not change with age Compared with all 18 samples the sum of the skinfolds averaged only a trifle over 70 per cent of the average of all 18 samples but this does not fully indicate the real difference in fatness Since about 1 5 mm of the skin plus subcutaneous fat layer is true skin about 6 mm of the sum of the skinfolds is not fat And since Σ skinfolds includes four layers of skin plus fat the average thickness of subcutaneous fat at the sites of measurement was only a trifle over 2 mm in these Japanese men whereas the average for all 18 samples was nearly twice that figure Compared with the fattest men in these studies the U S railroad employees the difference is impressive indeed — 2 vs 6.5 mm of subcutaneous fat the average subcutaneous fat thickness of these Japanese is less than a

TABLE C7 1

Median valu s for Japanese men classed by age and these values expressed as per centage of the average of the medians for all 18 samples of men

SAMPLE and VARIABLE	MEDIAN VALUES 40-44	45-49	50 54	55 59	MEDIAN as % of AVERAGE 40-44	45-49	50-54	55- 9
TANUSHIMAR J								
(no of men)	(112)	(117)	(137)	(143)	(112)	(117)	(137)	(143)
Height m	162	161	159	160	95 4	95 2	94 5	95 4
Relative Wt	89	86	84	84	90 7	89 4	88 2	89 3
Σ Skinfo ds mm	15	15	14	15	70 8	73 5	67 6	75 4
Systolic B P mm Hg	120	128	132	138	91 6	96 2	95 7	98 2
D astolic	68	70	72	78	84 0	86 0	86 3	92 5
Serum Cholesterol mg %	167	165	178	168	80 9	79 6	85 2	81 3
USHIBUKA								
(no of mer)	(115)	(128)	(139)	(118)	(115)	(128)	(139)	(118)
Height cm	160	160	158	159	94 2	94 6	93 9	94 8
Relative Wt	91	89	87	84	92 8	92 5	91 4	89 3
Σ Skinfolds mm	-	--	--	--	--	--	--	--
Systolic B P mm Hg	126	128	135	140	96 2	96 2	98 5	99 6
D astolic	75	76	80	80	92 6	93 4	95 9	94 9
Serum Choles erol mg %	142	143	137	144	68 8	69 0	65 6	69 7

TABLE C7 2

Cigarett sm king habits of men classed by age n Tanushimaru and Ushibuka Per- centage of men who had never smoked men who had quit smoking and heavy smokers (20 or more garettes daily)

AGE	TANUSHIMARU Never	Quit	Heavy	USHIBUKA Never	Quit	Heavy
40 44	15 6	12 8	40 4	15 8	8 8	42 9
45 49	14 8	12 2	49 5	10 9	4 7	49 6
50 54	13 8	13 8	44 7	13 1	8 8	35 7
55 59	20 1	13 7	39 6	20 3	6 8	31 2
40 59	16 2	13 2	43 4	14 9	7 2	37 7

TABLE C7 3

un ber me be (LO) and above (HI) age spec ic medians for all Japanese Tanushimaru Ushibuka right hand Hea y 20 or more Other 1 19 cigarettes per day

	Smok r LO	HI	Hea y LO	HI	Other LO	HI	on Smoker LO	HI	Heavy LO	HI	Other LO	HI
R l Wt		83	108	106	[illegible]	64	38	62	84	[illegible]	106	73
Skf		83	108	106	71	[illegible]						
(B P		[illegible]	100	164	[illegible]	66	38	7	99	[illegible]	110	89
D B P		[illegible]	102	[illegible]	[illegible]	61	[illegible]	33	[illegible]	93	112	87
S u n t u		[illegible]	115	94	53	74	5	[illegible]	93	91	96	103

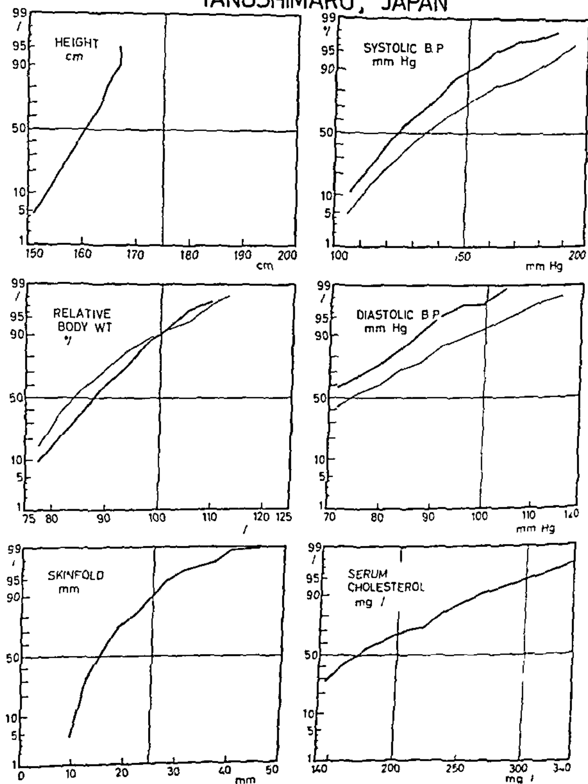

TANUSHIMARU, JAPAN
HEIGHT
cm
cm
SYSTOLIC B.P
mm Hg
mm Hg
RELATIVE
BODY WT
%
DIASTOLIC B.P
mm Hg
mm Hg
SKINFOLD
mm
mm
SERUM
CHOLESTEROL
mg %

Figure C7 1

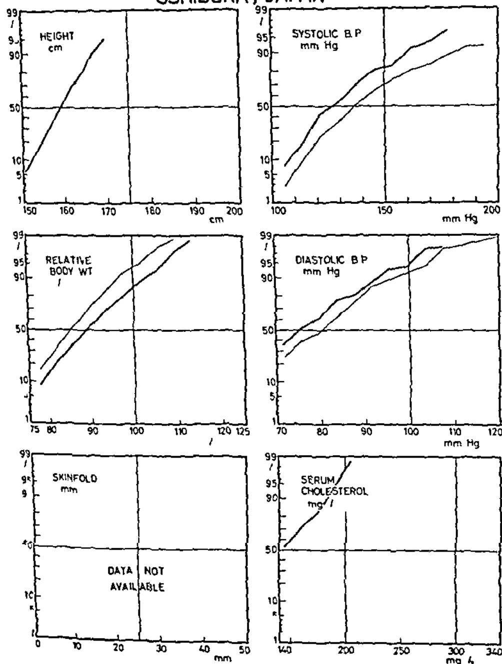

USHIBUKA, JAPAN
HEIGHT
cm
99
95
90
50
10
5
1
150
160
170
180
190
200
cm
SYSTOLIC B.P
mm Hg
100
150
200
mm Hg
RELATIVE
BODY WT
75
80
90
100
110
120
125
DIASTOLIC B.P
mm Hg
70
80
90
100
110
120
mm Hg
SKINFOLD
mm
DATA NOT
AVAILABLE
0
10
20
30
40
50
mm
SERUM
CHOLESTEROL
mg
140
200
250
300
340
mg

Figure C7.2

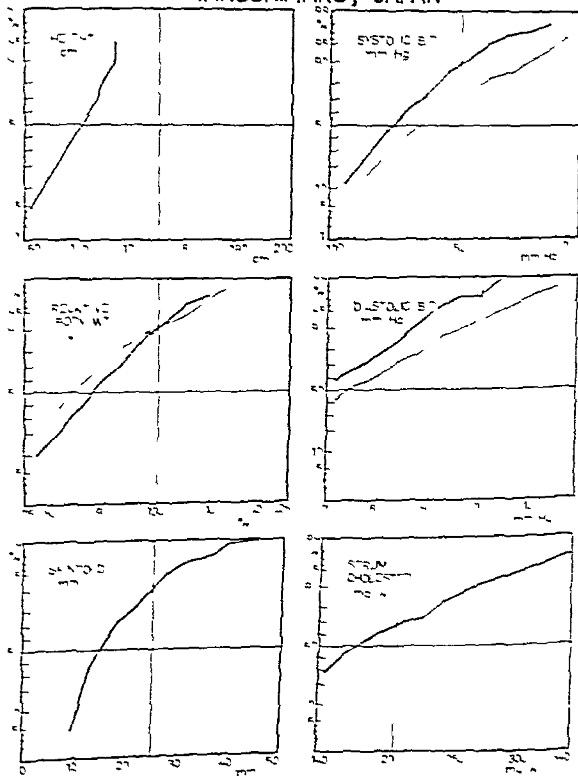


Figure C7 1

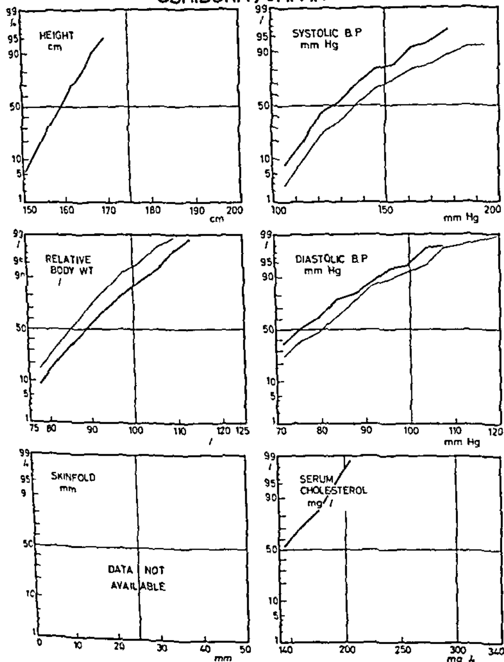

USHIBUKA, JAPAN
HEIGHT
cm
SYSTOLIC B.P
mm Hg
RELATIVE
BODY WT
DIASTOLIC B.P
mm Hg
SKINFOLD
mm
DATA NOT
AVAILABLE
SERUM
CHOLESTEROL
mg

Figure C7 2

third that of the Americans studied

Both in systole and in diastole the blood pressure tended to be appreciably higher at Ushibuka than at Tanushimaru many members of the same research team worked in both villages so this difference is unlikely to be due to differences between observers Serum cholesterol concentration though low in both areas was some 18 per cent (i e more than 25 mg per 100 ml on the average) higher in Tanushimaru than in Ushibuka Compared with the average of all 18 samples the serum cholesterol values were very low in both places and in this respect were approached only by the men in Velika Krsna Yugoslavia whose cholesterol values were a little lower than those of the Japanese fishermen and higher than those of the Japanese farmers

Smoking Habits

Heavy cigarette smoking has been the rule for men in Japan for many years In the present series of studies the Japanese proved to be the heaviest smokers of any of the groups studied at Tanushimaru 43 4 per cent of the men smoke 20 or more cigarettes daily and at Ushibuka 37 7 per cent are in that category Table C7 2 summarizes the smoking data

In contrast with most other samples in Japan there was no trend for the percentage of quit smokers to rise with age The percentage of men who never smoked was highest in the oldest age class and this is statistically significant but the percentage of never smoking is not age-related at other ages As in other samples the percentage of heavy smokers tends to fall with age

The men in these two villages differ significantly in the percentages of non-smokers versus smokers Tanushimaru having more non-smokers (chi-square = 6 486 p = less than 0 02) This is primarily because there are more quit smokers in Tanushimaru On the other hand the percentage of heavy smokers is higher in Tanushimaru than in Ushibuka but the difference is not quite significant (chi-square = 3.526 p = about 0 06)

Table C7.3 examines the question of associations between smoking habits and the measured variables The Tanushimaru men differ from men in most of the other samples studied in that differences in smoking habits are not significantly associated with differences in relative body weight or body fatness In Ushibuka the non-smokers as elsewhere, more often tended to be overweight for the distribution above and below the median relative body weight chi-square = 6 899 and p = less than 0 01

In Ushibuka but not in Tanushimaru non-smokers were overly represented in the above-median class of systolic blood pressure For systolic pressure 72 of the non-smokers were above the median but only 55 would be expected from chance the difference is highly significant (chi-square = 12 776 and p = less than 0 001)

In Ushibuka smoking habits were unrelated to serum cholesterol but in Tanushimaru the heavy smokers tended to have lower values than the rest of the men However when calculation is made with the median cholesterol value as cutting point the difference is not quite significant (chi-square = 3 199)

Electrocardiographic Findings

ECG data from Tanushimaru are presented in Tables C7 4 and C7 5 and from Ushibuka in Tables C7 6 and C7 7 The original records were not available for replicate and adjudicated readings in the central laboratory but were coded by Dr H Toshima in Ja-

TABLE C7 4

TANUSHIMARU JAPAN

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDII GS
(Rate per 1 000 men in parentheses)

ECC FINDL G	ECG Code		AGE GROUP (Number of Men) 40 44 (112)	45 49 (117)	50 54 (135)	55 59 (140)
Total with reportable ECG ite s	I	IX	39 (348 2)	39 (333 3)	48 (355 6)	54 (385 7)
Q Waves	I	1	2 (17 9)	1 (8 5)	0	0
		2	2 (17 9)	1 (8 5)	1 (7 4)	4 (28 6)
		3	0	0	0	0
Axis Deviation	II					
Left		1	1 (8 9)	0	2 (14 8)	1 (7 1)
Right		2	0	0	1 (7 4)	0
H gh Amplitude R Waves	III					
Left type		1	9 (80 4)	10 (85 -)	7 (51 9)	12 (85 7)
Right type		2	1 (8 9)	0	1 (7 4)	1 (7 1)
S T Depression (rest)	IV					
S T J 1 mm or more horiz or downward segment		1+4	2 (17 9)	2 (17 1)	2 (14 8)	3 (21 4)
S T J 0 5 1 mm horiz or downward segment		2	4 (35 7)	5 (42 7)	10 (74 1)	15 (107 1)
No S T J plus segment downward		3	6 (53 6)	3 (25 6)	9 (66 7)	7 (50 0)
T Wave Negativity (rest)	V					
5 mm or more		1	1 (8 9)	0	0	0
1 mm to 5 mm		2	0	0	0	2 (14 3)
0 ± 1 mm		3	3 (26 8)	0	7 (51 9)	7 (50 0)
A V Conduction Defect	VI					
Complete Block		1	0	0	0	0
Parti l Block		2	0	0	1 (7 4)	0
P R over 0 21 second		3	0	3 (25 6)	4 (29 6)	2 (14 3)
A c lerated Conduction		4	1 (8 9)	1 (8 5)	0	0
V ntricular Blocks	VII					
Left B ndle		1	0	0	0	0
Right Bundle		2	0	0	2 (14 8)	2 (14 3)
Incomplete Right Bundle		3	1 (8 9)	1 (8 5)	0	0
Intra ntricular Block		4	0	0	0	0
Arrhythmias	VIII					
Premat re Beats		1	0	0	0	0
V ntricular tachycardia		2	0	0	0	0
Atrial fibrillation, flutter		3	0	0	1 (7 4)	5 (35 7)
S pra v ri tachycardia		4	0	0	0	0
V ntricular rhythm		5	0	0	0	0
A V nodal rhythm		6	0	1 (8 5)	0	0
S tachycardia		7	1 (8 9)	0	0	1 (7 1)
S u b adycardia		8	11 (98)	13 (111 1)	14 (103 7)	9 (64 3)
T nically poor record	IX	8	0	0	0	0

TABLE C7 5

TANUSHIMARU JAPAN

FREQUENCY OF POST EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (107)	45 49 (109)	50 54 (127)	55 59 (127)
Exercise tests not made or incomplete	X 1 X 2	5 (44 6)	8 (68 4)	8 (59 3)	13 (92 9)
S T Depression post-exercise (none at rest)	XI				
S-T - J 1 mm or more horiz or downward segment	1+4	0	0	1 (7 9)	0
S T - J 0 5 - 1 mm , horiz or downward segment	2	2 (18 7)	3 (27 5)	3 (23 6)	5 (39 4)
No S-T J plus segment downward	3	3 (28 0)	0	2 (15 7)	3 (23 6)
T Wave Negativity post exercise (none at rest)	XII				
5 mm or more	1	0	0	0	0
1 to 5 mm	2	0	0	0	0
0 + 1 mm	3	0	0	0	1 (7 9)
Arrhythmias post-exercise (none at rest)	XV 1	0	0	1 (7 9)	1 (7 9)
Technically poor post-exercise records	XI 8	0	0	1 (7 9)	0

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

ECG FINDING	ECG Code	40-44	45 49	50 54	55 59
At Rest					
Large Q Waves	I 1	2 (17 9)	1 (8 5)	0	0
Lesser Q Waves with Negative T Waves	I 2 3 + V 1 2	0	0	0	0
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	0	C	2 (14 8)	2 (14 3)
S-T Depression as sole anomaly	IV 1-4 only	6 (53 6)	8 (68 4)	12 (88 9)	12 (85 7)
High Amplitude R with S-T Depression	III 1 + IV 1-4	1 (8 9)	1 (8 5)	3 (22 2)	5 (35 7)
Complete Heart Block	VI 1	0	0	0	0
Ventricular *Conduction Defect*	VII 1 2 4	0	0	2 (14 8)	2 (14 3)
Arrhythmias	VIII 2 6	0	1 (8 5)	1 (7 4)	5 (35 7)
Post exercise					
S T Depression as sole anomaly	XI 1 4 only	4 (37 4)	1 (9 2)	3 (23 6)	3 (23 6)
Negative T as sole anomaly	XII 1-3 only	0	0	0	0
Ventricular Conduction Defect as sole anomaly	XIV 1 2 4 only	0	0	0	0
Arrhythmias as sole anomaly	XV 1 only	0	0	1 (7 9)	0

TAB E C7 6

USHIBUKA JAPAN

FREQ CY OF RESTING ELECTROCARD OGRAPH C FINDINGS
(Rat per 1 000 men in paren heses)

EC F D G	ECG Code	AGE GROUP (Number of Men) 40 44 (112)	45 49 (122)	50 54 (13)	55 59 (114)
w pa abl					
EC s	I IX	31 (276 8)	46 (377 0)	46 (338 2)	37 (324 6)
Q W	I 1	0	0	1 (7 4)	1 (8 8)
	2	0	0	0	1 (8 8)
	3	0	0	0	0
A s De a	II				
Le	1	1 (8 9)	0	1 (7 4)	1 (8 8)
R g	2	0	0	0	0
g Am l e R Wa s	III				
Le b	1	20 (78 6)	14 (14 8)	18 (132 4)	19 (166 7)
R g r p	2	1 (8 9)	0	0	0
S T D p s (es)	IV				
S T 1 mm o mo e r z					
ow wa d s gm	1 4	1 (8 9)	3 (24 6)	1 (7 4)	0
S 0 5 mm o z or					
a d egm	2	1 (8 9)	7 (57 4)	6 (44 1)	5 (43 9)
S T J p segm d wnward	3	1 (8 9)	6 (49 2)	11 (80 9)	6 (52 6)
g s W (s	V				
mm m e	1	0	0	(7 4)	0
mm	2	8 9)	0	3 (22 1)	0
	3	0	4 (32 8)	(7 4)	3 (26 3)
A D	VI				
			0	0	
	2	8 9		(4 7)	(8 8)
A 2 s d o	3	26 8	5 (4 0	(7 4)	1 (8 8)
	4			0	
d k	VII				
				0	
P g n d	2	9	(24 6		(8 8)
c P	3		(8	0	0
			0	0	
A F P s	VIII				
			0	(7 4	(8 8
A La n				0	0
S	3				
	4				0
A 1		0			0
	6	0			0
S d	7	8	0		
	8	44	8	(6 8	3 (26 3
	IX 6				8 8

TABLE C7 5

TANUSHIMARU JAPAN

FREQUENCY OF POST EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40 44 (107)	45-49 (109)	50 54 (127)	55 59 (127)
Exercise tests not made or	X 1	5 (44 6)	8 (68 4)	8 (59 3)	13 (92 9)
incomplete	X 2				
S T Depression post-exercise					
(none at rest)	XI				
S T - J 1 mm or more horiz					
or downward segment	1+4	0	0	1 (7 9)	0
S T - J 0 5 - 1 mm , horiz or					
downward segment	2	2 (18 7)	3 (27 5)	3 (23 6)	5 (39 4)
No S-T J plus segment downward	3	3 (28 0)	0	2 (15 7)	3 (23 6)
T Wave Negativity post-exercise					
(none at rest)	XII				
-5 mm or more	1	0	0	0	0
-1 to -5 mm	2	0	0	0	0
0 + 1 mm	3	0	0	0	1 (7 9)
Arrhythmias post exercise	XV				
(none at rest)	1	0	0	1 (7 9)	1 (7 9)
Technically poor post exercise					
records	XI 8	0	0	1 (7 9)	0

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

At Rest					
Large Q Waves	I 1	2 (17 9)	1 (8 5)	0	0
Lesser Q Waves	I 2 3 +	0	0	0	0
with Negative T Waves	V 1 2				
Deeply Negative T as sole	V 1	0	0	0	0
anomaly	only				
Other Negative T as sole	V 2 3	0	0	[illegible] (14 8)	2 (14 3)
anomaly	only				
S T Depression as sole	IV 1 4	6 (53 6)	8 (68 4)	12 (88 9)	12 (85 7)
anomaly	only				
High Amplitude R	III 1 +	1 (8 9)	1 (8 5)	3 (22 2)	5 (35 7)
with S T Depression	IV 1-4				
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2 4	0	0	2 (14 8)	2 (14 3)
Arrhythmias	VIII 2 6	0	1 (8 5)	1 (7 4)	5 (35 7)
Post exercise					
S T Depression as sole	XI 1 4	4 (37 4)	1 (9 2)	3 (23 6)	3 (23 6)
anomaly	only				
Negative T as sole	XII 1-3	0	0	0	0
anomaly	only				
Ventricular Conduction Defect as	XIV 1 2 4	0	0	0	0
sole anomaly	only				
Arrhythmias	XV 1	0	0	1 (7 9)	0
as sole anomaly	only				

TABI E C7 6

USHIBUKA JAPAN

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FI IDINGS
(Rate per 1 000 men in parentheses)

ECG FI D G	ECG Cod		AGE GROUP (Number of M n) 40 44 (112)	45 49 (122)	50 54 (136)	55 59 (114)
T tal w t repo table ECG I e s	I IX		31 (276 8)	46 (3 7 0)	46 (338)	37 (324 6)
Q Wa e	I	1	0	0	1 (7 4)	1 (8 8)
		2	0	0	0	1 (8 8)
		3	0	0	0	0
Ax s Dev a on	II					
L f		1	1 (8 9)	0	1 (7 4)	1 (8 8)
R g t		2	0	0	0	0
H g Ampl tude R Waves	III					
Lef yp		1	20 (178 6)	14 (114 8)	18 (132 4)	19 (166 7)
R g type		2	1 (8 9)	0	0	0
S T D p a on (rest)	IV					
S T J 1 mm or mo e h r z wnwar s gme t		1+4	1 (8 9)	3 (24 6)	1 (7 4)	0
S T 0 5 mm hor z or d w war s gmer		2	1 (8 9)	7 (57 4)	6 (44 1)	5 (43 9)
N S T J plu gm nt dow ward		3	1 (8 9)	6 (49 2)	11 (80 9)	6 (52 6)
T Wa ega vity (r st)	V					
5 mm or mor		1	0	0	1 (7 4)	0
mm 5 mm		2	1 (8 9)	0	3 (22 1)	0
0 m		3	0	4 (32 8)	1 (7 4)	3 (26 3)
A C nd c on D f	VI					
C pl Block		1	0	0	0	0
P al Blo k		2	1 (8 9)	0	2 (14 7)	1 (8 8)
P R 0 2 s nd		3	3 (26 8)	5 (41 0)	1 (7 4)	1 (8 8)
A a a Conduc on		4	0	0	0	0
V lar block	VII					
L B le		1	0	0	0	0
R gh B l		2	2 (17 9)	3 (24 6)	0	1 (8 8)
L om l t R ght Bund		3	0	1 (8 2)	0	0
In nt ular Block			0	0	0	0
A mia	VIII					
P R at		1	0	0	1 (7 4)	1 (8 8)
al t n ca d		2	0	0	0	0
A llat n fl t r		3	0	0	0	0
S t hy a d a		4	0	0	0	0
V u r h thm		5	0	0	0	0
A n l hy hm		6	0	0	0	0
S a a hy rd a		7	1 (8 9)	0	0	0
S ad a d		8	(44 6)	8 (65 6)	5 (36 8)	3 (26 3)
T ll po ca d	IX	8	0	0	0	1 (8 8)

TABLE C7 7

USHIBUKA JAPAN

FREQUENCY OF POST-EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (92)	45-49 (102)	50 54 (117)	55 59 (98)
Exercise tests not made or incomplete	X 1 X 2	20 (178 6)	20 (163 9)	20 (147 1)	16 (140 4)
S T Depression post-exercise (none at rest)	XI				
S T - J 1 mm or more, horiz or downward segment	1+4	0	0	0	1 (10 2)
S-T - J 0 5 - 1 mm , horiz or downward segment	2	0	2 (19 6)	3 (25 6)	4 (40 8)
No S T-J plus segment downward	3	3 (32 6)	4 (39 2)	5 (42 7)	5 (51 0)
T Wave Negativity post-exercise (none at rest)	XII				
-5 mm or more	1	0	0	0	0
-1 to -5 mm	2	0	0	0	0
0 ± 1 mm	3	0	0	0	0
Arrhythmias post-exercise (none at rest)	XV 1	0	0	1 (8 5)	0
Technically poor post-exercise records	XI 8	0	0	0	0

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

	ECG Code	40-44	45-49	50 54	55 59
At Rest					
Large Q Waves	I 1	0	0	1 (7 4)	1 (8 8)
Lesser Q Waves with Negative T Waves	I 2 3 + V 1 2	0	0	0	0
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	0	1 (8 2)	0	1 (8 8)
S-T Depression as sole anomaly	IV 1-4 only	1 (8 9)	12 (98 4)	12 (88 2)	7 (61 4)
High Amplitude R with S-T Depression	III 1 + IV 1-4	1 (8 9	2 (16 4)	2 (14 7)	2 (17 5)
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2, 4	2 (17 9)	3 (24 6)	0	1 (8 8)
Arrhythmias	VIII 2-6	0	0	0	0
Post-exercise					
S T Depression as sole anomaly	XI 1-4 only	2 (21 7)	4 (39 2)	4 (34 2)	8 (81 6)
Negative T as sole anomaly	XII 1-3 only	0	0	0	0
Ventricular Conduction Defect as sole anomaly	XIV 1 2 4 only	0	0	0	0
Arrhythmias as sole anomaly	XV 1 only	0	0	1 (8 5)	0

pan and there may be systematic reading differences The Japanese ECG data are therefore considered with these reservations

At Tanushimaru three large Q waves (I 1) were seen curiously they were among men in the younger decade of age Axis deviation (II 1 2) was uncommon except that there was one case extremely rare of marked right axis deviation (over 120°) Left and right type of high amplitude R waves are comparatively common and the rates for resting S-T segment depression *alone or in combinations* are quite high The modified version of the S-T segment depression code in the Minnesota classification (see Appendix) in which "ischemic sagging depression is separated from categories IV 1 and XI 1 was not employed in these readings *Prolonged* P-R interval was unusually common but must be viewed in the light *of the finding* that ten per cent of the *Tanushimaru population* had resting heart rates less than 50 beats per minute

Post-exercise ECG records were obtained from 93 2 per cent of the men at Tanushimaru the exclusions being made for the following reasons 1) the resting ECG showed ST-T abnormality or ventricular *conduction disturbance* 2) there was difficulty in walking 3) blindness 4) *the examination* was done in hospital or at home not at the field station The "yield of additional ECG *abnormalities* from the post exercise record was low at Tanushimaru

At Ushibuka large Q waves (I 1) were rare and axis deviation was relatively uncommon Left type high amplitude R waves were recorded in 15 per cent of the men aged 40—59 years It is not known whether *this is primarily* due to a *systematic peculiarity* of reading or to the degree *to* which the finding is associated with *lean* body build or elevated blood *pressure* However the finding is twice as common in Ushibuka as in Tanushimaru where the ECG coder was the same individual

There was an unusually high prevalence of resting S-T depression (10 per cent in Codes IV 1—3) probably related to the same factors as in Tanushimaru The coincidence of frequent prolonged A-V conduction and sinus bradycardia was found in Ushibuka as in Tanushimaru Other arrhythmias were rare

Post exercise ECG records were obtained from 84 5 per cent of the men of Ushibuka the reasons for exclusion being the same as at Tanushimaru Again as at Tanushimaru the number of new ECG abnormalities from the exercise test was not large

The infrequency of conduction defects heart blocks and arrhythmias is notable in the records from Tanushimaru and Ushibuka There were no cases of complete block, intraventricular block left bundle branch block in rest there were only two cases of frequent extra-systoles six of atrial fibrillation or flutter and two of sinus tachycardia

Hypertension Prevalence and Other Variables

By any criterion hypertension is somewhat less prevalent in the Japanese villages than in the other areas studied The data for two criteria of diastolic blood pressure are summarized in Table *C7 8 With* either criterion hypertension was decidedly less prevalent *in* these villages than the average of the other population samples in these studies At ages *40—54* but not at ages 55—59 hypertension is more common at Ushibuka than at Tanushimaru For the total age range 40—59 years hypertension is significantly more prevalent at Ushibuka than at Tanushimaru if 95 mm or more in diastole is the cri-

TABLE C7 8

Prevalence of diastolic hypertension (95 or more 100 or more mm Hg fifth phase) among men classed by age Percentage of men at Tanushimaru and Ushibuka who are hypertensive compared with the average for all 18 samples of men

SAMPLE	40-44		45-49		50 54		55 59	
	95mm	100mm	95mm	100mm	95mm	100mm	95mm	100mm
Tanushimaru	1 8	1 8	3 4	3 4	7 3	6 6	15 4	10 5
Ushibuka	7 0	3 5	13 3	8 6	12 9	8 6	12 7	7 6
Mean 18 samples	13 6	7 9	15 6	8 9	20 9	13 5	21 5	13 8

TABLE C7 9

Prevalence of overweight (110 or more and 120 or more per cent of standard average for height and age) Percentage of men at Tanushimaru and Ushibuka classed by age who are overweight compared with the average for all 18 samples of men

SAMPLE	40 44		45 49		50 54		55 59	
	110%	120%	110%	120%	110%	120%	110%	120%
Tanushimaru	1 8	0	2 6	1 7	4 4	0 7	1 4	0 7
Ushibuka	4 7	0 9	2 6	0	1 6	0 8	0 9	0
Mean 18 samples	20 9	8 4	19 4	6 9	18 1	6 7	16 8	7 3

terion (chi square = 4.394 p = less than 0.04) with 100 mm or more as the criterion the two villages are not significantly different

The distributions of the hypertensive men defined as diastolic pressure of 95 mm or more into decile classes of relative body weight Σ skinfolds and serum cholesterol concentration are shown in Figures C7.3 and C7.4 At Ushibuka as in other samples reported here the prevalence of hypertension rises with increasing relative body weight Among the men in deciles 9 10 (i e the 20 per cent for relative weight) 18.7 per cent are hypertensive as compared with only 5.6 per cent among men in deciles 1 2 But Tanushimaru is remarkable in that there is no tendency for hypertension prevalence to vary with relative weight

On the other hand at Tanushimaru the prevalence of hypertension seems to be related to body fatness at least in the upper part of the Σ skinfolds distribution Compared with the lower 80 per cent (deciles 1—8) of the distribution of Σ skinfolds the men in the top 20 per cent of Σ skinfolds have 2.72 times the prevalence rate of hypertension and the difference is highly significant (chi square = 7.527 p = less than 0.01) Σ skinfolds data are not available for Ushibuka

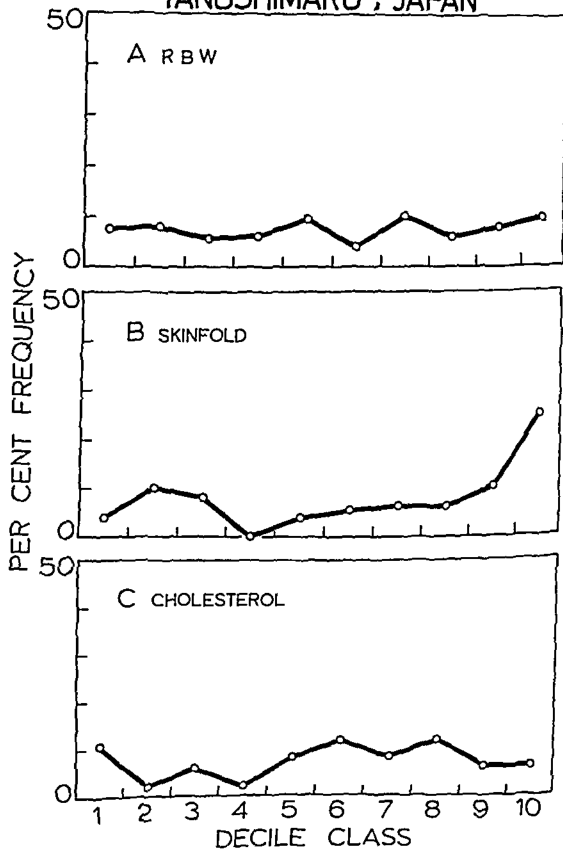
At Tanushimaru there is no significar relationship between hypertension and serum cholesterol level but at Ushibuka there is an irregular tendency for the prevalence of hypertension to be greater among the men with the relatively higher erum cholesterol values Comparing the men above the cholesterol median with those below the median at Ushibuka the respective prevalence figures are 33 cases among 246 men or 13.4 per cent and 24 cases among 247 men or 9.7 per cent This difference at the median cutting point does not reach stati tical significance but when the men in the top 20 per cent of serum chole terol are compared with the rest of the men their prevalence of hypertension proves to be significantly higher (chi-square = 4.012 p = less than 0.05)

Prevalence of Overweight and Other Variables

Data on the prevalence of overweight are given in Table C7.9 Both in Tanushimaru and Ushibuka only 2.4 per cent of the men aged 40—59 would qualify as overweight when this is defined as 110 or more per cent of the "standard" average body weight for height and age with the more commonly used cutting point of 120 or more per cent almost none of these men would be classed as overweight The distributions of the few overweight men (110 or more per cent of "standard" average) in these samples into decile classes of serum cholesterol and blood pressure are shown in Figures C7.5 and C7.6 In both villages and for all three variables there is some tendency for the prevalence of overweight to increase as the values of the other variables increase but statistical analysis is needed to evaluate this

The small numbers of overweight men hamper such analysis but comparison can be made of the men over the median with those below the median for these variables Since in these respects the distributions are not significantly different in the two samples it is reasonable to combine the da a represented in Figures C7.5 and C7.6

For Tanushimaru and Ushibuka combined the above median men in cholesterol have an overweight prevalence of 3.72 per cent the figure for the below-median men is 1.66 per cent but chi square is only 3.05 and p = about 0.08 Diastolic blood pressure however proves to be significant in the abo e- and below-median compari-


TANUSHIMARU, JAPAN
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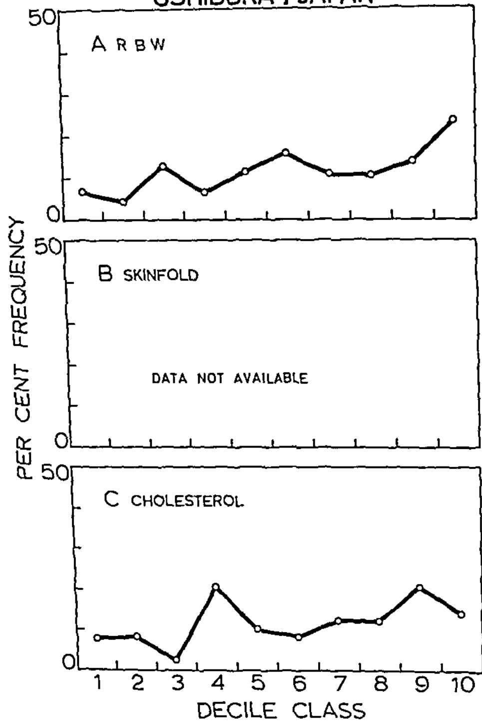
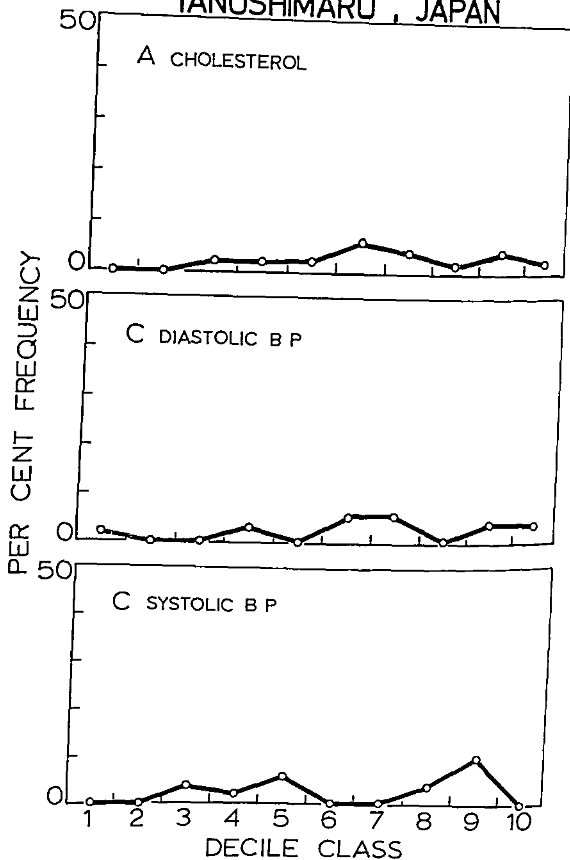
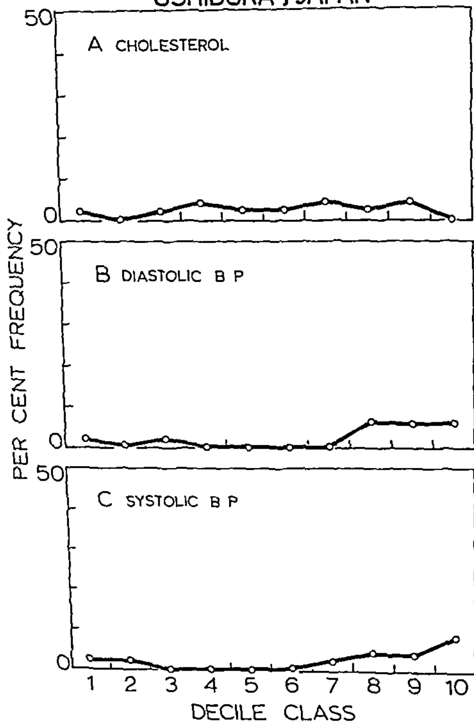
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS


USHIBUKA , JAPAN
50
A RBW
0
50
B SKINFOLD
DATA NOT AVAILABLE
0
PER CENT FREQUENCY
50
C CHOLESTEROL
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS



TANUSHIMARU , JAPAN
A CHOLESTEROL
C DIASTOLIC B P
C SYSTOLIC B P
PER CENT FREQUENCY
50
0
50
0
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS


USHIBUKA, JAPAN
A CHOLESTEROL
B DIASTOLIC B P
C SYSTOLIC B P
PER CENT FREQUENCY
50
0
50
0
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

son Among 505 men below the median diastolic blood pressure for their age and village only *5 were overweight* compared with 19 among 504 above-median men chi-square = 7 254 and p = *less than* 0 01 Similarly for systolic pressure among 505 men below the median there were 5 overweight men while among the 504 above-median men there were 19 cases of overweight

Prevalence of Obesity and Hypercholesterolemia

Classification systems for obesity (in terms of Σ skinfolds) and hypercholesterolemia are presented in Section H below Though these criteria based on the distributions of measurements in the "healthiest areas in the 18 population samples studied *are rigorous only 8* per cent of the Tanushimaru men would be classed in any grade of obesity and *only 2 per cent* would be classed as Grade 1 obesity In serum cholesterol concentration the Tanushimaru men are *less remarkable 9 per cent were Grade* 1 and 19 per cent Grade 4 hypercholesterolemia In Ushibuka only one per *cent of the men were Grade 4 hyper*cholesterolemia and no men were classed in higher grades

Summary

In the farming village Tanushimaru *and the fishing village* Ushibuka *in* southern Japan (Kyushu) 99 8 per cent of all men aged 40—59 were examined *(N = 1013) Compared with the men in* the other samples in these studies these men were shorter much lighter *thinner had* very low serum cholesterol values and tended to have lower blood pressures especially in *diastole* Compared with the fishermen of Ushibuka the farmers of Tanushimaru were similar in height and in relative body *weight tended to have slightly lower* blood pressures and significantly higher serum cholesterol values

Over *70* per cent of the men of Tanushimaru and almost 80 per cent of the men of Ushibuka smoked cigarettes The frequency of heavy smoking (20 or more cigarettes daily) was higher in these Japanese villages than in any of the other samples of men of this age studied Non-smokers at Ushibuka but not at Tanushimaru included an unduly high proportion of relatively overweight men and men with relatively high systolic blood pressure In neither area was there an unexpected frequency of relatively high serum cholesterol values among the non-smokers At Tanushimaru but not at Ushibuka heavy smokers included fewer men than expected with relatively high serum cholesterol values

Significant electrocardiographic ab*normalities* were similar and relatively uncommon in both Tanushimaru and Ushibuka Sinus tachycardia in rest was *unusually frequent in both villages*

The prevalence of hypertension in these villages was decidedly less than *the average for the other samples* of men in these studies At Ushibuka but not at Tanushimaru the prevalence of *hypertension rose with increasing* relative body weight At Tanushimaru the men with the highest Σ skinfolds most *often tended to have hypertension* Obesity was rare in these samples

Acknowledgments

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kami Osamu Tokura Hiroshi Kameo Masam ichi Akasu Kazuhiko Sasaki Taizo Endo Koki Matsutake Ikuro Goto Yoshie Ohya Hiroto Mashiba Hiroshi Okamuru Tsuyoshi Murakami Takeshi Sasaki Yasuhiko Nabeshima Eisaburo Yamagata Mikitoshi Horamatsu and Tadashi Koga

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C8 RAILROAD EMPLOYEES IN ROME

by H L Taylor, Mario Monti Vittorio Puddu Alessandro Menotti and Ancel Keys

In many countries employees of the railroads do rather similar work tend to be stable in their occupations and are covered by systems of disability retirement and record-keeping that make them especially suitable for epidemiological studies on cardiovascular diseases The example of the studies on railroad employees in the United States (see Section C1 above) led to the organization of a similar study on employees of the State Railways of Italy with concentration in regard to detailed medical examinations on certain occupational categories of male employees in Rome

The examinations were made in the summer of 1962 The methods were identical and professional personnel (Drs H L Taylor and H Blackburn) engaged in the work in the U S A participated in the work in Rome The eligible roster consisted of permanently employed men aged 40—59 who were in the selected job categories Actually many men on the list were not invited because of known conflicts in the operating schedules Among about 1 000 men aged 40—59 in the four selected occupations who were invited 806 were examined Some of those who did not respond were unable to do so because of local difficulties in getting to the examination headquarters in the Stazione Termini during the scheduled period so the effective response rate of those who really had an opportunity to respond was better than 80 per cent

In contrast to the United States all railroads in Italy are completely electrified and there are various other differences in technical operations and traditional working arrangements so it is not possible to equate job categories in the two countries Four occupations were covered in Rome 1) clerks including station masters (capi stazione) 2) switchmen 3) electricians and 4) maintenance of way men The distribution of men in the Rome sample by age and occupation is given in Table C8 1

The work of railroad clerks in Italy is generally similar to that in the United States but the study in Rome concentrated on station masters a subcategory of clerks These men report arrivals and departures of all trains and are on the platforms at the moment of arrival and departure More of the Italian clerks worked in small stations along the line than the clerks sampled in the United States By design the latter were confined to railroad centers where both clerks and switchmen are employed

There are some differences in the work of the switchmen in the two

TABLE C8 1

Numbers of Rome railway men classed by age occupation and location

OCCUPATION	IN ROME PROPER				OUTSIDE ROME PROPER			
	40-44	45-49	50-54	55-59	40-44	45-49	50-54	55-59
Clerks	16	19	15	10	29	33	28	15
Switchmen	17	35	27	10	21	20	23	9
Electricians	35	23	46	24	18	22	24	11
Maintenance of Way Men	15	16	18	7	13	46	48	38
All Men	83	93	106	51	111	121	123	73

TABLE C8 2

Rome railway men. Medians and the median values expressed as percentage of the averages of the medians for all 18 samples of men

VARIABLE	MEDIAN VALUES				MEDIAN as % of AVERAGE			
	40-44	45-49	50-54	55-59	40-44	45-49	50-54	55-59
Height cm	166	166	165	164	97 8	98 2	98 0	97 8
Relative Weight %	108	108	106	108	110 1	112 3	111 3	114 8
Σ Skinfolds mm	26	27	25	26	122 6	132 4	120 8	130 7
Systolic B P mm Hg	135	138	138	142	103 1	103 8	100 7	101 0
Diastolic B P mm HG	86	89	89	90	106 2	109 3	106 7	106 8
Serum Chol , mg %	207	206	209	204	100 3	99 4	100 0	98 7

countries In Italy the switching crews are smaller and more tailored in number to the needs of the immediate job

The railroad electricians in Italy have various tasks in the maintenance of the electrical system Up to the age of 45 or so they do a considerable amount of work on the overhead lines which involves climbing poles The electricians aged 50 and over work mainly on the ground As a result the younger electricians are probably more active than the switchmen but the older men are not

The men who maintain the road bed in Italy do a good deal of heavy work and observation of them at work gives the impression that their work is heavier than that of their counterparts in the United States

The Rome sample of men represents an area centered on the city proper the equivalent of a division in the American railroad system which extends to include the division points of Cassino 140 km Formia 180 km to the south Grossetto 180 km to the north and Sulmona 100 km to the southeast Though the job responsibilities are similar throughout the area living conditions and some of the working conditions in Rome itself differ from those outside of the capitol Table C8 1 distinguishes between Rome proper and the rest of the area in regard to age and occupation distribution

Distribution of Six Measured Variables

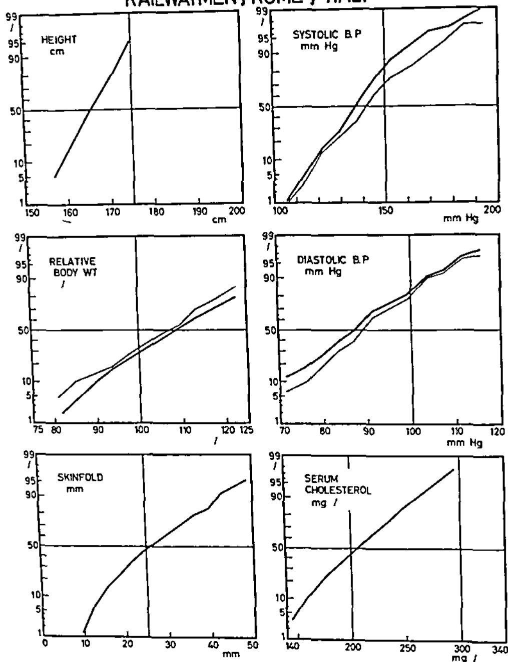
Table C8 2 gives the median values of height relative body weight the sum of the skinfolds (over the triceps muscle and over the tip of the scapula) systolic and diastolic (fifth phase) blood pressure and serum cholesterol concentration for all men in the Rome sample classed by age The table also expresses these values as percentages of the averages of the medians of all men of corresponding age in the 18 samples in this cooperative study

These Romans show no age trend in relative weight Σ skinfolds or serum cholesterol Height tends to decrease and blood pressure to rise with age these trends are similar to those found in other samples

Compared with the average of all samples the Rome railway men tend to be slightly shorter decidedly heavier at equal height and age and very much fatter they tend to have somewhat higher blood pressures especially in diastole, they correspond closely to the general average in serum cholesterol concentration The outstanding feature of these Romans is their tendency toward obesity as indicated by Σ skin folds Note that the true skin represents about 6 mm of the sum of the skinfolds so the median (all ages) actual subcutaneous fat thickness of these Romans is about 5 0 mm at these sites the corresponding figure for all 18 samples is about 3 6 mm so in this respect these Romans are nearly 40 per cent fatter than the general average of men studied They are in fact fatter than the men in any of the other samples expect the U S railroad employees

Compared with the other samples of men in Italy the Rome railway men are a little taller than the men in Montegiorgio some 4 cm taller than the men in Nicotera but several cm shorter than the men in Crevalcore They have considerably greater relative body weights and they are much fatter than the men in the other Italian samples At all ages they have somewhat higher serum cholesterol values than the other Italians studied though their cholesterol levels would be considered very low in the U S or in Finland

The cumulative frequency distributions of these variables on a probability scale are shown in Figure C8 1 In the graphs of relative body weight and blood pressure the heavy line is for ages



RAILWAYMEN, ROME, ITALY
HEIGHT
cm
cm
SYSTOLIC B.P
mm Hg
mm Hg
RELATIVE
BODY WT
%
DIASTOLIC B.P
mm Hg
mm Hg
SKINFOLD
mm
mm
SERUM
CHOLESTEROL
mg %
mg %

Figure C8 1

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TABLE C8 3

Cigarette smoking habits of Rome railway men classed by occupation and age
Percentage of non-smokers and of heavy smokers (20 or more cigarettes daily)

AGE	CLERKS		SWITCHMEN		ELECTRICIANS		MAINTENANCE	
	Non	Heavy	Non	Heavy	Non	Heavy	Non	Heavy
40-44	36 2	34 1	18 0	33 3	32 0	41 6	32 7	34 5
45-49	33 9	39 6	24 1	31 5	37 8	20 0	35 5	21 0
50-54	37 8	26 7	26 0	32 0	42 9	31 4	33 9	29 2
55 59	48 8	28 0	31 6	5 3	45 7	28 6	44 5	24 4
40 59	37 6	19 4	24 1	29 0	39 5	30 9	36 1	27 4

TABLE C8 4

Smoking Number of Rome railroad men below and above the age-specific median values (LOW and HIGH respectively) classed as NON-SMOKERS HEAVY (20 or more cigarettes daily) and OTHER (1-19 daily) smokers

VARIABLE	NON-SMOKERS		HEAVY		OTHER	
	LOW	HIGH	LOW	HIGH	LOW	HIGH
Relative Body Weight	99	167	144	85	139	131
Σ Skinfolds	107	159	135	93	140	129
Systolic B P	111	155	120	109	151	120
Diastolic B P	115	151	127	102	141	129
Serum Cholesterol	134	131	108	118	140	130

40—49 the light line for ages 50—59 for the other variables all ages 40—59 are combined Except for Σ skinfolds and systolic blood pressure, the distributions are reasonably "normal" The details of these distributions by 5-year age groups are given in the Appendix

Smoking Habits

In common with other men in Italy smoking among Rome railway men is confined to cigarettes almost none smoke pipes or cigars The majority of these Romans are cigarette smokers — 60 5 per cent (among electricians) is the lowest frequency of smoking the highest being 75 5 per cent (among switchmen) The smoking habits are summarized in Table C8 3 Though fewer switchmen had never smoked (10 5 per cent) all of the groups were similar in the frequency of heavy smoking (20 or more cigarettes daily) the range being only from 27 4 per cent for maintenance of way men to 30 9 per cent for electricians

Over the range 40—59 years smoking habits tend to change with age For all occupations combined the percentage of heavy smokers drops with increasing age from a high of 36 0 per cent heavy smokers at 40—44 to a low of 23 4 at age 55—59 The percentage of non-smokers rises with advancing age and this trend is statistically significant (comparing ages 40—44 with 55—59 chi-square = 5 179 and p = 0 025) But among smokers the trend to fewer heavy smokers at older ages is not significant for example comparing ages 40—44 with 55—59 chi-square = 1 606 those who continue to smoke do not change the intensity of their smoking as they grow older The tendency for non-smoking to become more common with increasing age is due to an increase in stopped smokers there is no trend in the percentage of men who never smoked to change with age but the increase in stopped smokers is significant comparing ages 40—44 with 55—59 the percentages of stopped smokers are 13 7 and 24 2 respectively and the difference is significant (chi square = 5 061 p = 0 025)

The Rome railroad men more often tend to be heavy smokers compared with the men in the rural samples in Italy The percentages of heavy smokers in the Rome Crevalcore Montegiorgio and Nicotera samples are 29 9 17 7 9 6 and 8 0 respectively Further considering only men who smoke among the Romans 45 9 per cent are heavy smokers while only 28 2 16.2 and 11 7 per cent in Crevalcore Montegiorgio and Nicotera respectively are in that category All of these differences are highly significant

Table C8 4 gives the distributions of the Rome railroad men specified as to smoking habits and classed as above and below the age-specific medians for relative body weight Σ skinfolds blood pressure and serum cholesterol concentration As in other samples the non-smokers tend to be relatively heavier fatter and to have higher blood pressures than the smokers All of these differences are statistically highly significant Differences in smoking habits are not associated with differences in serum cholesterol in these men

On the other hand the heavy smokers tend to be more often below the medians for all of these variables except serum cholesterol Compared with "other smokers the heavy smokers are more often underweight (chi-square = 6 097) but the differences in the other variables are not statistically significant

Electrocardiographic Findings

The electrocardiographic findings in Rome are summarized in Tables C8 5

TABLE C 8 6

RAILWAYMEN ROME, ITALY

FREQUENCY OF POST EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

		AGE GROUP (Number of Men)			
ECG FINDING	ECG Code	40 44 (193)	45 49 (208)	50 54 (220)	55 59 (118)
Exercise tests not made or incomplete	X 1 X 2	4 (20 3)	6 (28 0)	11 (47 6)	6 (48 4)
S T Depression post exercise (none at rest)	XI				
S T J 1 mm or more horiz or downward segment	1	1 (5 2)	0	5 (22 7)	2 (16 9)
S T J 0 5 - 1 mm horiz or downward segment	2	1 (5 2)	1 (4 8)	1 (4 5)	4 (33 9)
No S T J plus segment downward	3	1 (5 2)	0	2 (9 1)	0
S T J 1 mm or more upward segment	4	4 (20 7)	4 (19 2)	11 (50 0)	5 (42 4)
T Wave Negativity post exercise (none at rest)	XII				
5 mm or more	1	0	0	0	0
1 to 5 mm	2	0	1 (4 8)	3 (13 6)	2 (16 9)
0 + 1 mm	3	3 (15 6)	2 (9 6)	8 (36 4)	2 (16 9)
Arrhythmias post exercise (none at rest)	XV 1	0	0	0	1 (8 5)
Technically poor post exercise records	XI 8	8 (41 5)	4 (19 2)	7 (31 8)	7 (59 3)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

At Rest					
Large Q Waves	I 1	1 (5 1)	0	1 (4 3)	2 (16 1)
Lesser Q Waves with Negative T Waves	I 2 3 + V 1 2	0	0	0	0
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	5 (25 4)	5 (23 4)	1 (4 3)	2 (16 9)
S T Depression as sole anomaly	IV 1 4 only	0	3 (14 0)	1 (4 3)	0
High Amplitude R with S T Depression	III 1 + IV 1 4	0	0	0	1 (8 1)
Complete Heart Block	VI 1	0	0	0	0
Ventricular Conduction Defect	VII 1 2 4	1 (5 1)	0	6 (25 9)	2 (16 1)
Arrhythmias	VIII 2 6	0	1 (4 7)	1 (4 3)	0
Post exercise					
S T Depression as sole anomaly	XI 1 4 only	5 (25 9)	4 (19 3)	13 (59 1)	8 (67 8)
Negative T as sole anomaly	XII 1 3 only	2 (10 4)	0	4 (18 2)	3 (25 4)
Ventricular Conduction Def ct as sole anomaly	XIV 1 2 4 only	0	0	0	0
Arrhythmias as sole anomaly	XV 1 only	0	0	0	1 (8 5)

TABLE C 8 5

RAILWAYMEN, ROME ITALY

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (197)	45-49 (214)	50-54 (231)	55 59 (124)
Total with reportable ECG Items	I - IX	46 (233 5)	55 (257 0)	68 (294 4)	38 (306 5)
Q Waves	I 1	1 (5 1)	0	1 (4 3)	2 (16 1)
	2	4 (20 3)	3 (14 0)	4 (17 3)	1 (8 1)
	3	0	2 (9 3)	3 (13 0)	1 (8 1)
Axis Deviation	II				
Left	1	5 (25 4)	7 (32 7)	14 (60 6)	4 (32 3)
Right	2	0	0	3 (13 0)	0
High Amplitude R Waves	III				
Left type	1	6 (30 5)	9 (42 1)	7 (30 3)	4 (32 3)
Right type	2	0	0	0	0
S T Depression (rest)	IV				
S T - J 1 mm or more horiz or downward segment	1	0	2 (9 3)	0	3 (24 2)
S-T - J 0 5 - 1 mm horiz or downward segment	2	0	1 (4 7)	2 (8 7)	1 (8 1)
No S-T-J plus segment downward	3	0	1 (4 7)	0	1 (8 1)
S T - J 1 mm or more upward segment	4	0	0	0	0
T-Wave Negativity (rest)	V				
5 mm or more	1	0	0	0	0
- 1 mm to -5 mm	2	0	0	1 (4 3)	4 (32 3)
0 ± 1 mm	3	6 (30 5)	6 (28 0)	5 (21 6)	6 (48 4)
A-V Conduction Defect	VI				
Complete Block	1	0	0	0	0
Partial Block	2	0	0	0	0
P-R over 0 21 second	3	3 (15 2)	0	0	1 (8 1)
Accelerated Conduction	4	0	0	3 (13 0)	0
Ventricular Blocks	VII				
Left Bundle	1	0	0	0	0
Right Bundle	2	1 (5 1)	0	5 (21 6)	2 (16 1)
Incomplete Right Bundle	3	1 (5 1)	0	2 (8 7)	2 (16 1)
Intraventricular Block	4	0	0	1 (4 3)	0
Arrhythmias	VIII				
Premature Beats	1	1 (5 1)	0	1 (4 3)	1 (8 1)
Ventricular tachycardia	2	0	0	0	0
Atrial fibrillation flutter	3	0	0	0	0
Supra-vent tachycardia	4	0	0	0	0
Ventricular rhythm	5	0	0	0	0
A V nodal rhythm	6	0	1 (4 7)	1 (4 3)	0
Sinus tachycardia	7	4 (20 3)	6 (28 0)	4 (17 3)	0
Sinus bradycardia	8	2 (10 2)	0	1 (4 3)	0
Technically poor records	IX 8	5 (25 4)	3 (14 0)	2 (8 7)	1 (8 1)

TABLE C8 7

Prevalence of diastolic hypertension (95 or more 100 or more mm Hg fifth phase) among men classed by age Percentage among Rome railway men who are hypertensive compared with the average for all 18 samples of men

SAMPLE	40-44		45 49		50-54		55-59	
	95 mm	100 mm	95 mm	100 mm	95 mm	100 mm	95 mm	100 mm
Rome railway men	25 4	15 7	32 6	21 9	26 3	18 5	35 5	25 0
Mean 18 samples	13 6	7 9	15 6	8 9	20 9	13 5	21 5	13 8

TABLE C8 8

Prevalence of overweight (110 or more and 120 or more per cent of 'standard" average for height and age) Percentage of Rome railway men classed by age who are overweight compared with the average for all 18 samples of men

SAMPLE	40 44		45-49		50-54		55-59	
	110%	120%	110%	120%	110%	120%	110%	120%
Rome railway men	45 2	25 4	47 0	24 2	41 1	17 7	44 4	21 0
Mean 18 samples	20 9	8 4	19 4	6 9	18 1	6 7	16 8	7 3

and C8 6 Only four men showed clear evidence (Code I, 1) of old myocardial infarction The expectation from the findings on U S railroad employees of the same age would be 7 18 cases but the difference is not significant the numbers are so small that confidence limits are very wide Similarly, the prevalence of S-T depression and of negative T waves in rest is less than among the U S railroad men of the same ages but the differences do not reach statistical significance

In regard to ECG items of less interest in the present connection there were also no great differences between the railroad men in Rome and those in the United States Left axis deviation (Code II 1) was more common among the Romans but the difference is not statistically significant No case of A-V block occurred in either group Among 766 Romans not a single case of left bundle branch block (Code VII 1) was found while there were 12 cases among 2119 U S railroad employees (9 among 847 sedentary clerks) and this difference approaches statistical significance

The post-exercise records showed 18 cases of S-T depression (Code XI 1 2 3) among men who did not have this finding at rest thus bringing to 29 the total number of men with S-T depression in either rest or post-exercise There were 5 men with T wave inversion (Code V 1 2) in rest and 6 more were added post-exercise Compared with U S railroad employees these results are not significantly different

Prevalence of Hypertension and Other Variables

Men aged 40—59 employed by the Italian Railroad in Rome had a rather high prevalence 29 2 per cent of hypertension if a blood pressure of 95 mm or more in diastole (fifth phase) is the criterion This is to be compared with the rural samples in Italy — 2 9 per cent in Nicotera 11 3 per cent in Montegiorgio 23 5 per cent in Crevalcore The prevalence of diastolic hypertension at different ages is shown in Table C8 7

The difference between the Rome railroad employees and the men at Crevalcore is highly significant chi-square = 7 133 and p = less than 0 01 The prevalence rate for the Rome men is also substantially higher than the corresponding rates for the various classes of railroad employees in the United States However such comparisons must be made with reservations because the possibilities of considerable differences between observers cannot be ruled out (cf Section B2 above)

The distributions of the hypertensive Rome railroad men into their decile classes for relative body weight Σ skinfolds and serum cholesterol concentration are shown in Figure C8 2 There is a marked tendency for hypertension to become more prevalent as the values for each of these other variables increases and this is most dramatic for relative body weight and Σ skinfolds It is interesting to compare the prevalence of hypertension among men in the top 20 per cent (deciles 9 10) with those in the bottom 20 per cent (deciles 1 2) of the distributions of each of these variables For relative weight these prevalences are 47 1 and 12 4 per cent respectively for Σ skinfolds the figures are 50 3 and 12 4 for serum cholesterol 41 1 and 20 3 per cent All of these differences are highly significant

Overweight versus Other Variables

Table C8 8 shows the prevalence of overweight by two criteria among the men classed by age Overweight was

common among the Rome railroad men Taking 110 per cent or more of the average body weight for men of the same height and age in the Medico-Actuarial Investigations as the criterion 23.3 per cent of the railroad men in Rome were overweight This is to be compared with the samples of men of the same age in rural Italy — 18 1 per cent overweight in Nicotera 20 7 per cent in Montegiorgio 34 4 per cent in Crevalcore Among the samples of U S railroad employees the prevalence of this degree of overweight ranges from 26 to 37 per cent in the several occupations

The difference in prevalence of overweight between the Rome men and those in Crevalcore is highly significant but there is no significant difference in the comparison with Montegiorgio (chi-square = 1 278) The prevalence of overweight is significantly lower in Nicotera than among the Romans chi-square = 4 446 p = about 0 04

The distributions of these overweight railroad men in Rome into their decile classes for serum cholesterol and blood pressure are shown in Figure C8.3 Prevalence of overweight rises markedly with increasing values of these variables The men with the highest serum cholesterol values (decile 10) have an overweight prevalence of 67 per cent there is only 4 per cent overweight prevalence in the lowest cholesterol class the corresponding figures for men classed by diastolic blood pressure are 59 and 3 per cent among men in decile 10 in systolic pressure 57 per cent are overweight but in decile 1 the figure is 6 5 per cent The graphs in Figure C8 3 suggest that the relationships of the prevalence of overweight to the other variables are curvilinear upward

Men in Rome Proper and Men Outside the City

A comparison between the railroad men in Rome itself and those stationed outside the city is in effect a comparison between men in a great metropolis and men in the same jobs in small towns Table C8 9 makes this comparison in terms of the number of men in each of the four occupations above and below the age-specific median of all Rome railroad men for each of six variables

Among the 24 comparisons between men in the same occupation but working in Rome proper or outside the city only two show statistically significant differences and these both concern body fatness Switchmen outside Rome tend to be more often in the below-median class than expected — 23 cases observed 17.2 expected — and the difference has chi-square = 4 41 (p = less than 0 05) Maintenance of way men show the same trend more markedly — 38 men below 7 above the relative weight median — with chi-square = 7 96 (p = less than 0 01) These men tend to be the thinnest of all men in Rome but their counterparts outside the city are even thinner

In one other variable maintenance of way men outside Rome tend to differ from their counterparts in Rome outside Rome 30 of them are below and only 15 above the median the number expected from the distribution of all maintenance of way men being 24 0 The difference has chi square = 3 40 and p = less than 0 07

Comparisons Between Occupations

The clerks clearly tend to be more often overweight and fat than the men in the other occupations and this is true both in Rome proper and outside the city They also tend to be in the above-median class in both locations in all the other variables except serum cholesterol in the small group of clerks outside Rome The maintenance of way men tend to be distinguished from the rest

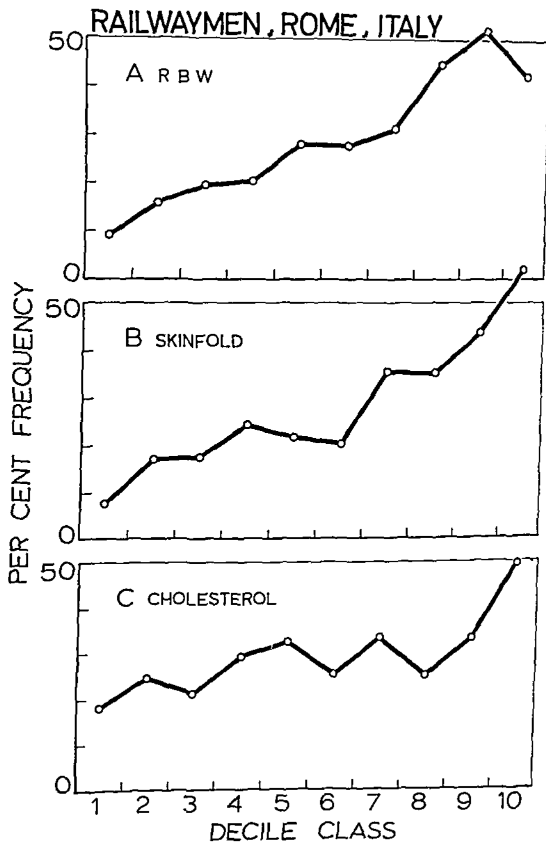

RAILWAYMEN, ROME, ITALY
A RBW
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
50
0
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

Figure C8 2

TABLE C8 9

Numbers of Rome Railway men above and below age-specific medians for all men by occupation and location Occupations are Clerks (CL) Switchmen (SW), Maintenance of Way men (MW) and Electricians (EL)

		ROME PROPER				OUTSIDE ROME PROPER			
Decile	N	CL	SW	MW	EL	CL	SW	MW	EL
Σ SKINFOLDS									
1-5	380	16	42	36	58	27	44	115	42
6-10	379	44	46	20	70	78	28	60	33
RELATIVE BODY WEIGHT									
1 5	380	24	44	31	64	44	40	95	38
6-10	381	36	45	25	64	61	33	80	37
SYSTOLIC BLOOD PRESSURE									
1-5	382	30	49	25	70	47	38	87	36
6-10	379	30	40	31	58	58	35	88	39
DIASTOLIC BLOOD PRESSURE									
1-5	380	29	50	27	58	40	47	96	33
6-10	381	31	39	29	70	65	26	79	42
SERUM CHOLESTEROL									
1-5	383	24	43	32	62	53	43	97	29
6-10	374	35	44	24	66	52	30	78	45
STANDING HEIGHT									
1-5	381	16	63	34	58	38	48	95	29
6-10	380	44	26	22	70	67	25	80	46

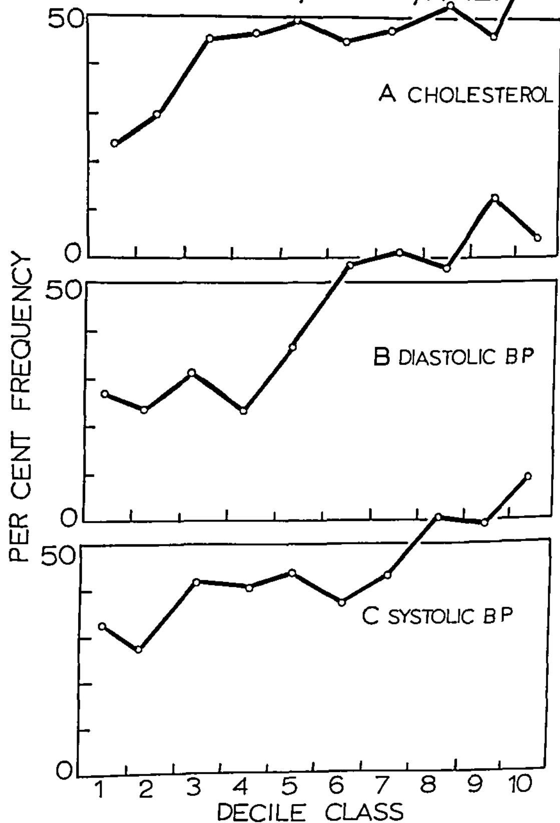

RAILWAYMEN, ROME, ITALY
50
0
A CHOLESTEROL
50
0
B DIASTOLIC BP
50
0
C SYSTOLIC BP
PER CENT FREQUENCY
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

TABLE C8 10

Number of clerks compared with switchmen plus electricians (SW + EL) in the distribution above and below (HIGH and LOW, respectively) the age-specific medians of six measured variables of all Rome railroad men O = observed, E = expected Chi-Square values (one degree of freedom) calculated from all four cells of the 2 x 2 tables

VARIABLE	OCCUPATION	LOW		HIGH		CHI-SQUARE
		O	E	O	E	
Σ Skinfolds	Clerk	43	71 6	122	93 4	28 21
	SW + EL	186	157 4	177	205 6	
Relative Wt	Clerk	68	79 1	97	85 9	3 96
	SW + EL	186	174 9	179	190 1	
Systolic B P	Clerk	76	83 7	89	81 3	n s
	SW + EL	193	185 3	172	179 7	
Diastolic B P	Clerk	69	80 0	96	85 0	3 89
	SW + EL	188	177 0	177	188 0	
Serum Cholesterol	Clerk	77	78 9	87	85 1	n s
	SW + EL	175	173 1	185	186 9	
Height	Clerk	53	78 1	112	86 9	21 36
	SW + EL	198	172 9	167	192 1	

of the railroad employees in being underweight, thin and having low cholesterol values, they are not significantly different in regard to blood pressure In regard to height, the maintenance of way men tend to be a little taller than the switchmen but shorter than the clerks and the electricians

For estimation of probabilities of differences between occupations it seems reasonable to compare all clerks with all switchmen and electricians ignoring location Comparisons of the number of men in these two occupational categories found to be above and below the age-specific medians are summarized for six variables in Table C8 10

There are no significant differences in systolic blood pressure or serum cholesterol but there are significant differences in all of the other variables The most striking findings are the tendencies of the clerks to be fatter and taller than the switchmen and electricians It is interesting that the difference in relative body weight is barely significant ($p = 0\ 05$) in spite of the sharp difference in body fatness The bodies of the switchmen and electricians must have much more bone and muscle than those of the clerks

At all ages the maintenance of way men are thinner than the men in any of the other occupations the average Σ skinfolds being 23 7 mm , S E $= \pm 0\ 7$ compared with the next thinnest men the switchmen whose average was 25 5 $\pm 0\ 8$ mm But in relative body weight the order of these two groups is reversed the averages being 106 6 $\pm$ 1 0 per cent for maintenance of way men and 105 5 $\pm$ 1 2 for switchmen This suggests that the switchmen are less muscular than the men who maintain the roadbed

In several respects the clerks and electricians on the one hand tend to differ from the switchmen and maintenance of way men on the other The men in the former group tend to be relatively heavier, fatter have higher blood pressures and serum cholesterol values For example the mean (and S E) values ages 40—59 for serum cholesterol are 208 9 $\pm$ 3 3 and 213.5 $\pm$ 2 8 mg per 100 ml for clerks and electricians respectively, the corresponding values for switchmen and maintenance of way men are 202.3 $\pm$ 3 1 and 202 7 $\pm$ 2 5, respectively In the standard excercise test the recovery pulse rate too seemed to differentiate the occupations in the same way, averages being 106 6 $\pm$ 1 1 and 100 9 $\pm$ 1 1 beats per minute for clerks and electricians, respectively and 968 $\pm$ 1 2 and 96 3 $\pm$ 1 0 for switchmen and maintenance of way men respectively

Salary Differences

The salaries of the Rome railroad employees in the occupations covered in the present study are highest for the station masters and lowest for the maintenance of way men the lowest paid of the latter having only about 56 per cent of the salary of the most highly paid station masters But in general the salary differentials are not very large Roughly the pay of the maintenance of way men averages around two-thirds that of the station masters the corresponding figures for the switchmen and electricians being more like three-fourths of the station masters' salaries

Such differentials are not enough to mean that the men in the different occupations are grossly different in economic status But costs of living have been rising in Italy and the margin between bare necessity and actual income is certainly substantially larger for the station masters than for the other employees and they also have a higher social status As in other samples socioeconomic status tends to be inversely correlated with the physical activity on the job

C9 MEN IN VELIKA KRSNA, A SERBIAN VILLAGE

by Božidar S Djordjevic (Belgrade) Vladan Josipovic (Belgrade) Srecko I Nedelkovic (Belgrade) Toma Straser (Belgrade) Vladimir Slavkovic (Belgrade) Božidar Simic (Belgrade) Ancel Keys (Minneapolis) and Henry Blackburn (Minneapolis)

Introduction

During the survey of the rural men in Corfu in 1961 representatives of the Faculty of Medicine of Belgrade University acted as observers On their return to Yugoslavia interest developed in conducting parallel studies in Serbia with identical methods and arrangements to this end were made which in effect brought the Belgrade team into the program of cooperative studies reported here

Velika Krsna a village south of Belgrade was selected to initiate the program in Serbia Velika Krsna was chosen because the size of the popula tion is suitable it is within easy access by automobile from Belgrade and yet it is relatively isolated and untouched by industry and tends to remain a typical Serbian farming village of the older type The plan was to organize a parallel study in another area of Serbia where the more primitive form of agri culture is giving way to a state planned development of light industry This second study is in fact now in operation at Zrenjanin north of Belgrade but the data from the initial examinations became available too late to be included in the present report

As elsewhere in Yugoslavia registry of the population is an important feature of the political and economic organization so it was not difficult to compile a roster of all men aged 40 through 59 Among a total of 571 men in the roster 552 (or 96 7 per cent) were examined in the fall of 1962 During the examinations and the subsequent analysis of the data some cases of error in age were discovered and the number of men whose data are here reported is 510

Among these men the percentages in the age classes 40—44 45—49 50—54 and 55—59 were respectively 26 7 15 8 26 5 and 31 0 The peculiarity of this age structure with an excess in the oldest class and a marked shortage of men aged 45—49 is not easily explained The loss of men in World War II should have been greatest among the youngest men those aged 17—22 at the start and 22—27 at the end of the war in their country After the war migration of Velika Krsna men to nearby Belgrade and other industrial centers should also be expected to involve the younger more than the older men While these considerations make it understandable that the oldest men were the most numerous in 1962 the

Summary

In the equivalent of a railroad division centered at Rome Italy 806 men aged 40—59 long-time employees of the Italian railroad system were examined Of these men 22 5 per cent were clerks 22 2 per cent switchmen 27 8 per cent electricians and 27 5 per cent maintenance of way men The clerks are relatively sedentary the maintenance of way men generally do heavy physical work, and the switchmen and electricians tend to be intermediate in physical activity

Compared with the average of all men in the samples in these studies these men tended to be slightly shorter to have greater relative body weights somewhat higher blood pressures and to be much fatter they corresponded closely to the general average for serum cholesterol Compared with the men in the three samples in rural Italy the Rome railroad men were much fatter more often overweight and had higher serum cholesterol values

Most of these men smoked cigarettes with little difference among occupations The non-smokers among them tended to be relatively heavier and fatter and to have higher blood pressures than the smokers

The frequency of electrocardiographic abnormalities in the Rome sample is a little lower than in the U S railroad samples but the difference is not statistically significant

The prevalence of hypertension among these Romans was much higher than in the rural Italian samples and was relatively high by any criterion There was a marked tendency for the prevalence of hypertension to rise with increasing relative weight and Σ skinfolds there was a similar but less striking relationship to serum cholesterol concentration

Overweight was common among these Romans but the prevalence was not as high as in one of the rural samples of Italy The prevalence of overweight rose greatly with increasing blood pressure and serum cholesterol values

Comparison of the men in Rome proper and those stationed elsewhere in the area showed a significant difference only in respect to body fat the men in Rome itself tended to be fatter than the men outside the city

Comparisons between occupations within the railroad industry showed the clerks to have the highest values for relative body weight Σ skinfolds and blood pressure being followed next by the electricians in these variables In serum cholesterol the electricians were highest with the clerks second In all of these variables the switchmen and maintenance of way men were similar

Acknowledgments

The survey team in Rome included the following professional personnel Drs B Floris P Marroni and L Struglia

Dr Aldo Bellini the Ministry of Transport provided advice regarding the samples of men

Dr Flaminio Fidanza the Institute of Human Physiology University of Naples was responsible for the analysis of serum cholesterols

Miss Anna Bonanome provided conscientious assistance as secretary The staff of the Stazione Termini of Rome gave enthusiastic support to the project

TABLE C9 1

Mediansfor men at Velika Krsna and these values expressed as percentage of the average of the medians for men in all samples

VARIABLE	MEDIAN				MEDIAN AS % OF AVERAGE			
	40 44	45 49	50 54	55 59	40-44	45 49	50-54	55 59
Height cm	171	170	168	168	100 7	100 5	99 8	100 2
Relative Weight	89	88	88	86	90 7	91 5	92 4	91 4
Σ Skinfolds mm	13	13	13	12	61 3	63 7	62 8	60 3
Systolic B P mm	124	128	130	130	94 7	96 2	94 9	92 5
Diastolic B P mm	78	80	80	80	96 3	98 3	95 9	94 9
Serum Chol mg %	154	157	159	155	74 6	75 7	76 1	75 0

TABLE C9 2

Cigarette smoking habits of men of Velika Krsna Percentage of men who never smoked who had stopped who smoked 1-9 10 19 20 or more cigarettes daily at the time of their examination

SAMPLE	AGE	NEVER	QUIT	1-9	10 19	20 OR MORE
Velika Krsna	40 44	40 5	11 0	5 1	29 4	14 0
	45 49	43 3	8 6	11 1	16 0	21 0
	50 54	37 0	11 9	11 1	27 4	12 6
	55 59	43 5	10 9	10 3	25 0	10 3
	40 59	40 9	10 8	9 3	25 4	13 6

TABLE C9 3

Smoking Number of men in Velika Krsna Yugoslavia below (LOW) and above (HIGH) the age specific medians for age and area of measured variables classed according to smoking habits HEAVY 20 or more OTHER 1 19 cigarettes daily

VARIABLE	SAMPLE	NON SMOKERS		HEAVY		OTHER	
		LOW	*HIGH*	*LOW*	*HIGH*	*LOW*	*HIGH*
Relative Weight	Velika Krsna	119	144	33	35	101	75
Σ *Skinfolds*		112	151	31	37	110	66
Systolic B P		126	137	33	36	94	82
Diastolic B P		118	145	31	37	103	73
Serum Cholesterol		144	119	29	40	81	95

disproportions between the numbers in the 40—44 and 45—49 year-old classes is unexplained

The identity of methods and criteria at Velika Krsna with those in the other studies in this cooperative program was assured by the experience of Professor B S Djordjevic and Dr V Josipović in the survey at Corfu in 1961 and by the presence at the start of the work at Velika Krsna of Professor Ancel Keys and Dr Henry Blackburn of Minneapolis and Dr Gunnar Blomqvist of Stockholm

Distribution of Measured Variables

Table C9 1 gives the median values by age of relative body weight the sum of the skinfolds (over the triceps muscle and over the scapula) systolic and diastolic (fifth phase) blood pressure and serum cholesterol concentration The table also expresses these values as percentages of the averages of the medians of all men of corresponding age in the 18 samples in the present cooperative study

In height the Velika Krsna men show the usual slight age trend and correspond closely to the average for all samples In relative body weight they also show a slight age trend but they are relatively seldom overweight at any age This is understandable in view of the fact that they tend to be definitely thin The median sum of skinfolds is only 13 mm in the three younger age classes and only 12 mm at ages 55—59 After allowing for the relatively invariable thickness of the true skin the measurements indicate a median value for subcutaneous fat thickness of only 3 to 4 mm This may be compared for example with the corresponding value for 13 to 14 mm for U S railway clerks who are in this sense about four times (i e 400 per cent) fatter than the men of Velika Krsna The blood pressure shows a slight tendency to rise with age but in general the blood pressure is lower than the average of all the men in 18 samples and this difference is most pronounced at the oldest age

Serum cholesterol concentration at Velika Krsna shows no age trend in these ages and is remarkably lower than even in the Japanese men at Tanushimaru but not quite as low as in the fishermen at Ushibuka Japan

Cumulative frequency distributions of these variables on a probability scale are shown in Figure C9 1 Departure from the straight line of a normal distribution on this scale is as in other samples notable in the distribution of the sum of the skinfolds Height is normally distributed and the other variables are not grossly non-Gaussian in distribution The details of these distributions are given in tables in the Appendix

Smoking Habits

In Velika Krsna fewer men (48 3 per cent) smoke cigarettes and more men had never smoked (40 9 per cent) than in any of the other samples in the present cooperative study Only 13 6 per cent of the Velika Krsna men were heavy smokers i e 20 or more cigarettes daily In the percentage of men who never smoked the nearest approaches to Velika Krsna are Dalmatia (30 0) U S sedentary clerks (27 2) and Slavonia (26 4 per cent) it is notable that all three of the Yugoslav samples are in the list of the four samples with the largest proportion of men who had never smoked The distribution by age of the men according to smoking habits is given in Table C9 2

Some relationships between smoking habits and other variables are summarized in Table C9 3 which shows the number of men above and below the age-specific medians of the indicated variables for all Velika Krsna men As

in other samples of middle-aged men in these studies non-smokers at Velika Krsna tend to differ from smokers in being more often relatively overweight and fat The non smokers also tend to have higher blood pressures than the smokers

Serum cholesterol concentration seems to have a relationship to smoking habits according to the data in Table C9.3 However there is a curious discrepancy in regard to serum cholesterol between men at Velika Krsna who never smoked and those who stopped smoking which is concealed in Table C9.3 Among "never" smokers 121 men had cholesterol values below the cholesterol median while only 87 men were above that median The corresponding distribution of stopped smokers is 23 men below and 32 above the median The discrepancy between numbers of never smokers above and below the median is highly significant (chi-square = 5 23 p = 0 02) and of course the difference between never and stopped smokers is even less possible to ascribe to chance No such difference between never and stopped smokers is found in regard to the other variables at Velika Krsna nor in fact in any of the other areas studied A more general discussion of smoking habits and other variables is given in Section F below

Electrocardiographic Findings

Tables C9 4 and C9 5 summarize the electrocardiographic findings at Velika Krsna Five records showed the major Q wave picture (Code I 1) considered to represent definite old myocardial infarction The prevalence of 9 8 per thousand for this finding is relatively high but in contrast among the Velika Krsna men the prevalence of S-T and T wave abnormalities is very low as are in fact any other serious abnormalities Furthermore the exercise tests produced a very small yield of additional ECG abnormalities — only one case of S-T depression and no negative T waves larger than 1 mm

At Velika Krsna the most common ECG abnormality was high amplitude R waves left type (Code III 1) The frequency however is not surprising in these thin men most of whom do heavy physical work If these high R waves are discounted the total frequency of significant ECG findings is extremely low at Velika Krsna

The Prevalence of Hypertension

The data on prevalence of hypertension are summarized in Table C9 6 The prevalence of hypertension is low at Velika Krsna by any criterion — systolic pressure 140 mm Hg or more or 160 or more diastolic pressure of 95 or more or 100 or more At all ages and with either systolic pressure criterion the men of Velika Krsna consistently exhibited a lower frequency of hypertension than the men in any of the other samples in these studies For all ages 40—59 only 6 5 per cent has systolic pressures of 160 or more only 5.3 per cent had diastolic pressures of 100 or more

The prevalence of hypertension rose with age as expected Using 95 mm or more in diastole as the criterion hypertension was 51 per cent more common at ages 55—59 than at ages 40—44 The distributions of these hypertensive men into the decile classes for their ages of relative body weight the sum of the skinfolds and serum cholesterol are shown in Figure C9 2

In these figures the absence of relationships between hypertension and the other variables would be indicated by points randomly distributed about a horizontal trend line These graphs do in fact correspond to the picture of lack of relationship for the sum of the skin-

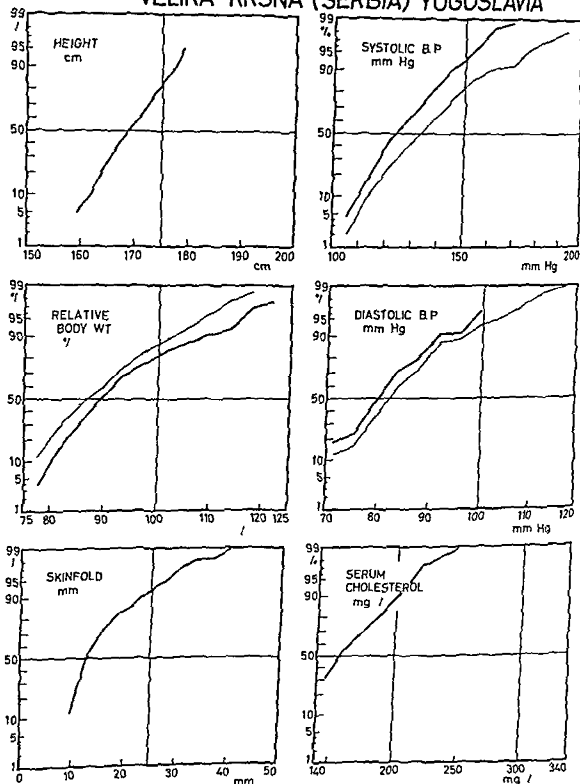

VELIKA KRSNA (SERBIA) YUGOSLAVIA
HEIGHT
cm
SYSTOLIC B.P
mm Hg
RELATIVE
BODY WT
%
DIASTOLIC B.P
mm Hg
SKINFOLD
mm
SERUM
CHOLESTEROL
mg %

Figure C9 1

TABLE C9 5

VELIKA KRSNA (SERBIA) YUGOSLAVIA

FREQUENCY OF POST EXERCISE ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1 000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40 44 (136)	45 49 (82)	50 54 (133)	55 59 (157)
Exercise tests not made or	X 1				
incomplete	X 2	0	0	2 (14 8)	0
S T Depression post exercise (none at rest)	XI				
S T J 1 mm or more horiz or downward segment	1	0	0	1 (7 4)	0
S T J 0 5 1 mm horiz or downward segment	2	0	0	0	0
No S T J plus segment downward	3	0	0	0	0
S T J 1 mm or more upward segment	4	1 (7 4)	1 (12 2)	3 (22 6)	5 (31 8)
T Wave Negativity post exercise (none at rest)	XII				
5 mm or more	1	0	0	0	0
1 to 5 mm	2	0	0	0	0
0 ± 1 mm	3	0	0	2 (15 0)	1 (6 4)
Arrhythmias post exercise (none at rest)	XV 1	1 (7 4)	2 (24 4)	1 (7 4)	11 (70 1)
T chnically poor post exercise records	XI 8	1 (7 4)	1 (12 2)	2 (15 0)	4 (25 5)

FREQUENCY OF CERTAIN ECG FINDINGS AND COMBINATIONS OF CLINICAL IMPORT

At R st					
Large Q Waves	I 1	0	0	2 (14 8)	3 (19 1)
Lesser Q Waves with Negative T Waves	I 2 3 + V 1 2	0	0	0	0
Deeply Negative T as sole anomaly	V 1 only	0	0	0	0
Other Negative T as sole anomaly	V 2 3 only	0	0	0	0
S T Depression as sole anomaly	IV 1 4 only	0	1 (12 2)	0	0
High Amplitude R w th S T Depression	III 1 + IV 1 4	0	1 (12 2)	3	2 (12 7)
Compl t Heart Block	VI 1	0	0	0	0
Ventr ular Conduction Defect	VII 1 2 4	0	0	0	6 (38 2)
Arrhythmias	VIII 2 6	0	2 (24 4)	2 (14 8)	2 (12 7)
Post exerc se					
S T D pression as sole anomaly	XI 1 4 only	1 (7 4)	1 (12 2)	3 (22 6)	1 (25 5)
N gative T as sole anomaly	XII 1 3 only	0	0	2 (15 0)	0
Ventricular Conduction Defect as sole anomaly	XIV 1 2 4 only	0	0	0	0
Ar hythmias as sole anomaly	XV 1 only	1 (7 4)	1 (12 2)	1 (7 5)	7 (44 6)

TABLE C9 4

VELIKA KRSNA (SERBIA) YUGOSLAVIA

FREQUENCY OF RESTING ELECTROCARDIOGRAPHIC FINDINGS
(Rate per 1,000 men in parentheses)

ECG FINDING	ECG Code	AGE GROUP (Number of Men) 40-44 (136)	45-49 (82)	50 54 (135)	55 59 (157)
Total with reportable ECG Items	I - IX	47 (345 6)	32 (390 2)	64 (474 1)	61 (388 5)
Q Waves	I 1	0	0	2 (14 8)	3 (19 1)
	2	1 (7 4)	1 (12 2)	1 (7 4)	2 (12 7)
	3	3 (22 0)	0	0	1 (6 4)
Axis Deviation	II				
Left	1	6 (44 1)	1 (12 2)	4 (29 6)	6 (38 2)
Right	2	0	0	0	0
High Amplitude R Waves	III				
Left type	1	11 (80 9)	11 (134 1)	22 (163 0)	18 (114 6)
Right type	2	0	0	0	0
S T Depression (rest)	IV				
S T - J 1 mm or more horiz or downward segment	1	0	0	0	1 (6 4)
S T - J 0 5 - 1 mm horiz or downward segment	2	1 (7 4)	0	4 (29 6)	0
No S-T-J plus segment downward	3	0	1 (12 2)	0	1 (6 4)
S T - J 1 mm or more upward segment	4	0	1 (12 2)	0	0
T-Wave Negativity (rest)	V				
5 mm or more	1	0	0	0	0
- 1 mm to -5 mm	2	0	0	2 (14 8)	2 (12 7)
0 ± 1 mm	3	2 (14 7)	2 (24 4)	4 (29 6)	4 (25 5)
A V Conduction Defect	VI				
Complete Block	1	0	0	0	0
Partial Block	2	0	0	0	0
P-R over 0 21 second	3	0	0	0	1 (6 4)
Accelerated Conduction	4	0	0	0	0
Ventricular Blocks	VII				
Left Bundle	1	0	0	0	2 (12 7)
Right Bundle	2	0	0	0	4 (25 5)
Incomplete Right Bundle	3	1 (7 4)	0	2 (14 8)	0
Intraventricular Block	4	0	0	0	0
Arrhythmias	VIII				
Premature Beats	1	0	0	2 (14 8)	4 (25 5)
Ventricular tachycardia	2	0	0	0	0
Atrial fibrillation flutter	3	0	2 (24 4)	0	2 (12 7)
Supra-vent tachycardia	4	0	0	1 (7 4)	0
Ventricular rhythm	5	0	0	0	0
A-V nodal rhythm	6	0	0	1 (7 4)	0
Sinus tachycardia	7	3 (22 0)	1 (12 2)	3 (22 2)	1 (6 4)
Sinus bradycardia	8	1 (7 4)	1 (12 2)	3 (22 2)	1 (6 4
Technically poor records	IX 8	0	0	1 (7 4)	0

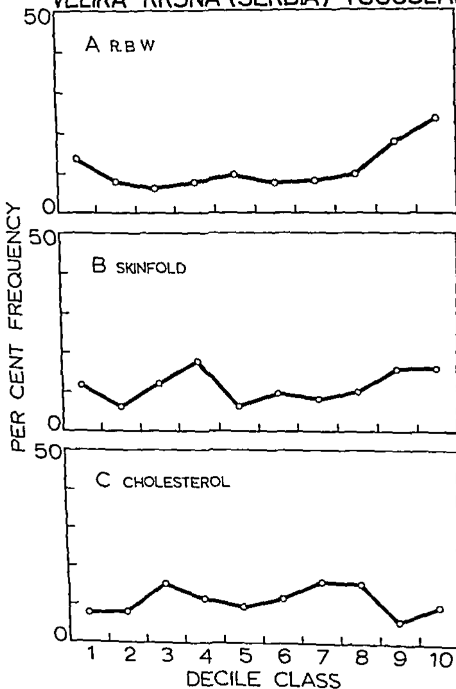
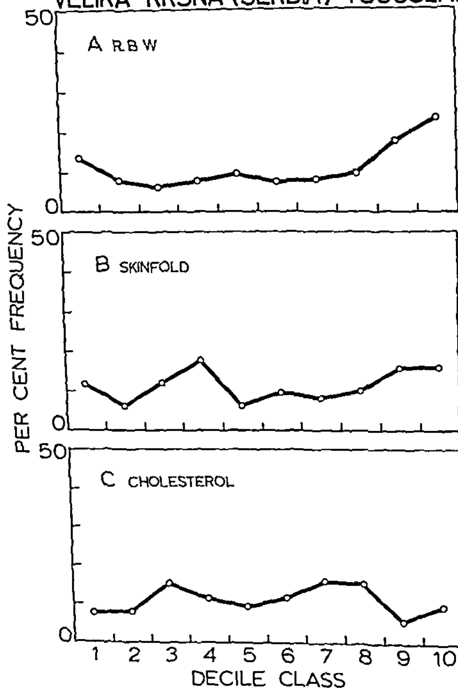
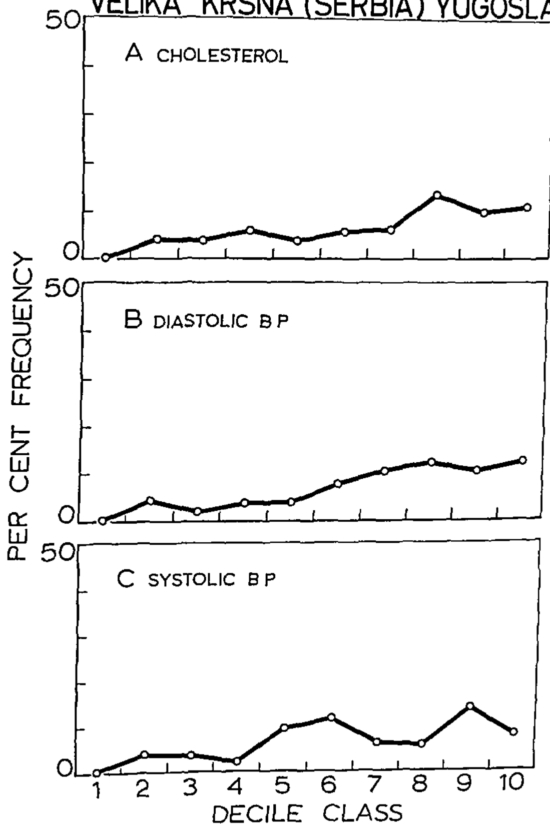

VELIKA KRSNA (SERBIA) YUGOSLAVIA
A R.B.W
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
1
2
3
4
5
6
7
8
9
10
DECILE CLASS

TABLE C9 6

Prevalence of hypertension and overweight among men in Velika Krsna Yugoslavia Percentages of men classed by criteria Systolic B P 140 or more and 160 or more Diastolic B P 95 or more and 100 or more mm Hg Relative body weight 110 or more and 120 or more per cent

SAMPLE	*AGE*	*NO* MEN	*SYSTOLIC* 140	160	*DIASTOLIC* 95	100	*OVERWEIGHT* 10%	20%
Velika Krsna	40-44	136	11 8	1 5	8 8	3 7	9 6	2 2
	45-49	82	23 2	3 7	9 8	3 7	9 8	2 4
	50-54	135	28 1	8 1	11 9	5 2	4 4	1 5
	55-59	158	40 5	10 8	13 3	7 6	3 8	1 3


VELIKA KRSNA (SERBIA) YUGOSLAVIA
A RBW
B SKINFOLD
C CHOLESTEROL
PER CENT FREQUENCY
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS


VELIKA KRSNA (SERBIA) YUGOSLAVIA
A CHOLESTEROL
B DIASTOLIC B P
C SYSTOLIC B P
PER CENT FREQUENCY
50
0
1 2 3 4 5 6 7 8 9 10
DECILE CLASS

folds and serum cholesterol For relative body weight it appears that hypertension is unduly common in the top deciles i e among the men in the top 20 or top 10 per cent of the relative weight distribution

Prevalence of Overweight

It was noted above that the men of Velika Krsna tend to have low relative body weights However there are some cases of overweight in that sample The data are shown in Table C9 6 If 110 or more per cent of the standard average body weight for height and age is the criterion only 4 8 per cent of Velika Krsna men are overweight The distributions of the overweight men with relative body weight of 110 or more per cent into the decile classes for their ages of serum cholesterol and blood pressure are shown in Figure C9 3

Obviously there is a definite trend for the prevalence of overweight to increase with increasing values of all three of these other variables The numbers are small but the trends seem to be roughly linear

Summary

In the fall of 1962 a study was made of 552 men aged 40—59 in the Serbian farming village of Velika Krsna Methods and criteria were identical with those in the other surveys in the co-operative studies reported in this monograph The men examined represented 96 7 per cent of all men of these ages in Velika Krsna

Data are presented on height relative body weight body fatness (sum of skinfold thicknesses over the triceps muscle and over the tip of the scapula) smoking habits and electrocardiographic findings on 510 men Compared with the averages for all samples of men in these studies the men of Velika Krsna are of medium height relatively underweight markedly thin seldom hypertensive and have strikingly low serum cholesterol concentrations Apart from 5 men with old myocardial infarction electrocardiographic abnormalities were relatively uncommon at Velika Krsna

Smoking is less common at Velika Krsna than in the other samples Compared with smokers the non smokers at Velika Krsna have higher relative body weights and thicker skinfolds and tend to have higher blood pressures

Hypertension at Velika Krsna shows little relationship to body fatness or serum cholesterol but is most common among men in the top 20 per cent of the relative body weight distribution Overweight is rare in Velika Krsna The prevalence of overweight increases with increasing serum cholesterol and with increasing blood pressure

Acknowledgments

The work at Velika Krsna was aided by grants from the Serbian Ministry of Health and its Council for Research and was much helped by Internal Medicine Clinic B and the Medical Faculty of the University of Belgrade by the Serbian Institute for Medical Investigations and by the local authorities of the village of Velika Krsna

The team who conducted the work at Velika Krsna was headed by Prof Bozidar S Djordjević and included Doctors Borica Balog Ljubica Bozinovic Vladan Josipovic Veronika Macarol Petar Milutinovic Srecko Nedeljkovic Aleksander Simic Božidar Simic Vladimir Slavkovic Gradimir Stojanovic Tomas Straser and Nurse Desa Lovric Advice and assistance at the start of the work were provided by Prof Ancel Keys and Doctors Henry Blackburn and Gunnar Blomqvist

D PHYSICAL ACTIVITY, OCCUPATION AND SOCIO-ECONOMIC STATUS

Introduction

In many populations where there are large socio-economic differences between classes coronary heart disease is reported to be much less common in the laboring class than in the middle and upper classes Though most of these reports suffer from defects of sampling and many of them raise questions about criteria a real difference in susceptibility can scarcely be doubted Because this contrast in susceptibility between socio-economic classes is commonly associated with obvious differences in the average level of physical activity it is tempting to conclude a cause and effect relationship

But in these populations the socio-economic classes also differ in many other respects — differences in the incidence of infectious and parasitic diseases in housing and exposure to thermal stresses in medical care in the quantity and character of the diet and often in the use of alcohol and tobacco Even differences in emotional status and "stress" may be suggested though this is only speculation

In Great Britain where such socio-economic differences are less extreme but not negligible an important etiological role of physical activity *per se* has been proposed on the basis of statistical studies of mortality records and autopsy reports (Morris *et al* 1953, Morris and Crawford 1958 Morris 1962) Some evidence in apparent confirmation has been reported from elsewhere Physicians' reports in one study in the U S A indicated that sedentary townsmen are more prone to myocardial infarction than farmers who are more active physically (Zukel *et al* 1959) In a cross-sectional survey in rural Finland it was found that lumberjacks who do very heavy physical work have fewer abnormal electrocardiograms than other Finnish men of the same age (Karvonen *et al* 1961)

However many studies in countries where socio-economic contrasts are not extreme have produced equivocal or even contradictory results (Chapman *et al* 1957 Spain and Bradess 1957 Forssman and Lindegaard 1958 Stamler *et al* 1960 Paul *et al* 1963) H L Taylor (1962) has reviewed this question and pointed out the difficulty in drawing valid conclusions from the evidence available at present

Obviously the question of the possible role of physical activity in the etiology of coronary heart disease requires much more study One approach is to compare men who differ in occupations and in habitual physical activity in regard to the distribution of other characteristics presumed to be associated with differences in susceptibility to the dis-

ea_e The data in the present investigations are relevant

The study of U S Railroad employees deliberately selected specific occupations which were presumed to require different degrees of physical activity A major feature of the study design was to compare clerks with switchmen who are comparable in economic status but who differ in physical activity Comparisons of railroad employees in different occupations presented in Section C1 above failed to show important differences in the variables of concern here but it should be noted that detailed studies of the work of the men in these several occupations in the railroads indicated that the differences in physical activity are not as large as had been expected These questions are discussed in Section C1 above

Within the population samples studied in Europe there are larger differences in both physical activity and socio economic status than between the railroad occupations studied in the U S A However in these populations the differences in physical activity are related to occupation and tend to be associated with substantial differences in economic circumstance and mode of life in other respects including the diet In these samples the subjects were classified in respect to both occupation and habitual physical activity and the analysis below will examine both factors Some of the data were briefly considered above in Sections C2—C6 inclusive

Comparison of activity or occupational groups in regard to relative body weight Σ skinfolds blood pressure and serum cholesterol in these series are readily made by observing the distribution of the men in the decile classes of the measured variables It will be recalled that in each area all men in each quinquennial age group were classed in respect to each variable of measurement into 10 groups or decile classes of equal size the 10 per cent of men with the lowest relative body weight being in decile class 1 for that variable and so on Accordingly since each man was thereby classed in comparison with all of the other men of his age in the same area the decile classification has the same relative meaning for men in all age groups and in all areas This fact allows combination of men of different ages and even in different areas in order to provide numbers adequate for statistical analysis

The measured variables considered here are relative body weight body fatness (Σ skinfolds) arterial blood pressure and serum cholesterol In relation to coronary heart disease the upper ends of the distributions of these variables are of greatest interest Accordingly attention will be focussed on the upper 30 per cent (deciles 8—10) and top 10 per cent (decile 10) of the age- and sample-specific distributions

A natural grouping of samples emerges from consideration of the frequency of coronary heart disease in the several areas In this respect the two Finnish samples and the men of Zutphen are distinguished from the samples in Croatia rural Italy and Greece Another grouping would be based on general economic status of the areas interestingly this consideration leads to the same separation — Finland and the Netherlands on the one hand Croatia rural Italy and Greece on the other These two groupings labelled A and B respectively for convenience are used in the subsequent analysis

Physical Activity — Socio Economic Status Ignored

Tables D1 and D2 summarize the observed versus the expected (chance) frequency of high values of the several variables "high" being the upper 30 per cent (deciles 8—10) of the distribu-

TABLE D1

Men with HIGH values (deciles 8-10) for the variables indicated, distributed by physical activity in East and West Finland and in Zutphen Among all men in these samples, 13 4 31 8, and 54 8 per cent were in Activity Classes 1, 2, and 3 respectively Numbers of men expected = the distribution if physical activity were unrelated

VARIABLE	TOTAL N HIGH	N OBSERVED HIGH % OF EXPECTED Act 1	Act 2	Act 3
Relative Weight	728	144 5	109 7	83 5
Σ Skinfolds	736	174 4	108 1	77 1
Systolic B P	721	108 7	95 2	100 7
Diastolic B P	718	119 5	103 4	93 3
Serum Cholesterol	728	114 8	93 3	100 3

TABLE D2

Men with HIGH values (deciles 8-10) for the variables indicated distributed by physical activity in Dalmatia Slavonia, Crevalcore, Montegiorgio Crete and Corfu Among all men studied in these areas 10 9 22 5 and 66 6 per cent were in Activity Classes 1 2 and 3 respectively Numbers of men expected = the distribution if physical activity were unrelated

VARIABLE	TOTAL N HIGH	N OBSERVED HIGH, % OF EXPECTED Act 1	Act 2	Act 3
Relative Weight	1260	163 9	122 0	82 1
Σ Skinfolds	1245	185 7	122 5	78 4
Systolic B P	1273	123 9	110 7	92 5
Diastolic B P	1263	128 5	112 6	91 1
Serum Cholesterol	1240	124 3	119 0	89 6

tions The trend is similar in both groups of samples the least active men are most apt to be relatively high in all of the five variables in both groups of samples In terms of the degree of departure of observation from chance expectation Σ skinfolds and relative body weight are most striking but the concetrations of high values for systolic and diastolic blood pressure and serum cholesterol in Activity Class 1 are also statistically significant except for systolic blood pressure in the A group of samples

On the other hand the men characterized by the highest physical activity are under-represented in deciles 8—10 of these variables and this discrepancy too is significant for all variables for sample group B and for samples A + B combined though not for systolic blood pressure or serum cholesterol in the A group of samples considered alone

Table D3 concerns the question as to whether high values of the measured variables are more common among sedentary men (Activity 1) than among moderately active men (Activity 2) The answer is yes for all variables and the difference is statistically significant for all variables expect serum cholesterol (chi square = 3 59 p = 0 06) and systolic blood pressure (chi square = 3 41 p = 0 07)

Tables D1—D3 concern the men in the top 30 per cent of the distributions Table D 4 summarizes the analysis of the data for the top 10 per cent (decile 10) of the distributions when men in Activity Class 1 are compared with those in Class 2 Among the men in Activity Class 1 the number observed to be in decile 10 of relative body weight is 21 1 per cent in excess of the expectation from the proposition that the relative weight distribution is similar in these two activity classes The comparable figure for deciles 8—10 of relative weight is 22 4 per cent excess in Activity Class 1

The data in Table D4 suggest that the influence of physical activity on the distribution of men with high values increases as we go to greater extremes of the variables of Σ skinfolds and blood pressure but does not change in regard to relative weight or serum cholesterol

Consideration of Socio-Economic Status

The apparent significance of physical activity indicated in Tables D1—D4 is of course confounded with other factors that tend to be associated with differences in physical activity in these populations It is notable that the major contribution to the differences related to physical activity in the fore-going data is made by the men in Activity Class 3 But most of these men are in a lower socio-economic class than the rest of the men The question then is how to eliminate or at least to reduce the confounding effect of variability in socio-economic status in examing the relationship between physical activity and the tendency to have high values of the variables of interest

Consideration of occupation offers some help Among the various occupations (see Occupation Code in the Appendix) those coded 1—13 generally connote a higher socio-economic status in these populations than the average of the rest of the occupations (Code numbers 14—94 excluding number 93 student which is not represented at these ages) These are professional men executives government officials (not including the lower civil service) proprietors land owners etc They include almost no men in Activity Class 3 but they are not all sedentary and from questioning them at the time of examination they were placed in Clas-

TABLE D3

Number of men with high values (deciles 8-10) observed (O) and expected (E) if physical activity were unrelated All 9 samples summed "TOTAL N" = total men in all deciles 1-10 in Activity Classes 1 and 2

VARIABLE	ACTIVITY 1		ACTIVITY 2		TOTAL
	O	E	O	E	N
Relative Weight	366	298 9	600	667 1	2508
Σ Skinfolds	424	320 5	596	699 5	2530
Systolic B P	277	256 4	535	555 6	2505
Diastolic B P	292	264 3	556	583 7	2535
Serum Cholesterol	280	259 4	548	568 6	2455

TABLE D4

Distribution of men with highest values (decile 10) into physical Activity Classes 1 and 2 compared with the distribution of men with high values (deciles 8 10) *Table entries are numbers of men observed* expressed as percentages of the numbers expected if physical activity played no role

VARIABLE	*DECILES 8 10*		*DECILE 10*	
	Act 1	Act 2	Act 1	Act 2
Relative Weight	122 4	89 9	121 1	90 5
Σ Skinfolds	132 3	85 2	144 8	79 4
Systolic B P	108 0	96 3	11, 8	9[illegible] 7
Diastolic B P	110 5	95 3	120 9	90 6
Serum Cholesterol	107 9	96 4	107 4	96 6

ses 1 or 2 according to their description of their work and recreation This last statement requires qualification the interviewers in the field were not always careful to ask searching questions about the actual physical activity when time was pressing there was a tendency to automatically assign farmers to Class 3 and professional men to Class 1 As a result distinction between physical activity and socio-economic status is blurred and any independent contribution of socio-economic status that may appear in the subsequent analysis will be under estimated

With these reservations an obvious approach is to compare men in the same activity class but differing in socio-economic status as judged by occupation Another approach is to compare men in different activity classes but in the same *general* socio-economic classification Because even Occupations 1—13 cover a wide range of socio economic status this last approach will probably over-estimate the independent significance of physical activity

Physical Activity versus Socio Economic Status

The analysis of physical activity and of socio economic status as factors related to the distribution of men into age- and area specific decile classes of the measured variables is illustrated by the example of relative body weight of the men in Activity Classes 1 and 2 in East Finland West Finland and Zutphen (group A of samples) The data are given in detail in Table D5

In this example there are two results

1) When occupational class is constant the men in Activity Class 1 compared with those in Class 2 who were observed to have high relative body weight (in the top 30 per cent of the age- and area specific distribution of relative weight) numbered 141 while the chance expectation is 127 6 men The excess is 10 5 per cent and activity alone is not significant (chi square = 3 10 p = 0 08)

2) When physical activity class is constant the men in Occupation Classes 1—13 compared with those in Classes 14—94 who were observed to have high relative weight numbered 128 while the chance expectation is 93 2 men The excess is 37.3 per cent and occupational status alone is very highly significant (chi-square = 26 43 p = much less than 0 001)

Table D6 summarizes the analysis made as in Table D5 of physical Activity Class 1 vs Class 2 occupational class constant and of Occupations 1—13 vs 14—94 physical activity class constant *in respect to the distribution* of the men in the A group of samples into the age- and area-specific deciles 1—7 and 8—10 for the five measured variables Compared with Activity Class 2 the men in Activity Class 1 include excessive numbers of men with high values in all variables but the observed distribution is significantly different from chance expectation only in the case of Σ skinfolds When the men in Occupations 1—13 are compared with those in Occupations 14—94 the excess *numbers* observed tend to be larger and the deviations from expectations are statistically significant *in all* variables except blood *pressure* Table D7 gives the same analyses for the B *group of samples* Again the picture is similar

Table D8 further condenses the data and gives the observed numbers of men in deciles 8—10 as percentages of the numbers expected Table D8 also gives the chi-square *values* for the distributions *In regard to relative* body weight *and Σ skinfolds* the segregation of relatively *overweight* and obese men by the *occupation* classification is consider-

TABLE D5

Physical Activity Class 1 vs Class 2 compared with Occupational Classes 1-13 vs 14-94 in regard to the distribution of men with high relative body weight (age- and area-specific deciles 8-10) Sample group A (East and West Finland Zutphen) O = observed number E = expected number

LINE	ACTIVITY CLASS	OCCUP CLASS	DECILES 1-7 O	DECILES 1-7 E	DECILES 8-10 O	DECILES 8-10 E	DECILES 1 10 O	DECILES 1 10 %
1	1	1-13	56	59 9	70	66 1	126	51 64
2	2	"	60	56 1	58	61 9	118	48 36
3	1+2	"	116		128		244	100 00
4	1	14 94	127	136 5	71	61 5	198	23 02
5	2	"	466	456 5	196	205 5	662	76 98
6	1+2	'	593		267		860	100 00
7	1	L 1+L 4	183	190 4	141	127 6	324	
8	2	L 2+L 5	526	512 6	254	267 4	780	
9	1	1-13	56	71 2	70	54 8	126	38 89
10	1	14 94	127	111 8	71	86 2	198	61 11
11	1	1-94	183		141		324	100 00
12	2	1-13	60	79 6	58	38 4	118	15 13
13	2	14-94	466	446 4	196	215 6	662	84 87
14	2	1-94	526		254		780	100 00
15	L 9+L 12	1-13	116	150 8	128	93 2	244	
16	L 10+L 13	14-94	593	558 2	267	301 8	860	

TABLE D6

Physical Activity Class 1 vs Class 2 compared with Occupational Classes 1-13 vs 14 94 Summarized from calculations as in Table D5 Sample Group A (East Finland West Finland Zutphen)

VARIABLE	ACTIVITY CLASS	OCCUP CLASS	DECILES 1-7 O	DECILES 1-7 E	DECILES 8-10 O	DECILES 8-10 E
Relative Weight	1	Constant	183	196 4	141	127 6
"	2	"	526	512 6	254	267 4
Relative Weight	Constant	1 13	116	150 8	128	93 2
" "	"	14-94	593	558 2	267	301 8
Σ Skinfolds	1	Constant	158	190 6	172	139 4
'	2	"	540	507 4	253	285 6
Σ Skinfolds	Constant	1-13	106	143 1	143	105 9
" "	"	14 94	592	554 9	282	319 1
Systolic B P	1	Constant	223	236 7	105	101 3
'	2	'	542	528 3	218	221 7
Systolic B P	Constant	1-13	178	170 6	71	68 4
' "		14-94	587	594 4	252	254 6
Diastolic B P	1	Constant	212	221 3	115	105 8
'	2	"	550	540 7	236	245 2
Diastolic B P	Constant	1 13	161	166 8	87	81 2
'		14-94	601	595 2	264	269 8
Serum Cholesterol	1	Constant	211	218 4	112	104 6
"	2		538	530 6	216	223 4
Serum Cholesterol	Constant	1 13	150	167 7	96	78 3
' '		14 94	599	581 3	232	249 7

TABLE D7

Physical Activity Class 1 vs. Class 2 compared with Occupational Classes 1-13 vs 14-94 Summarized from calculations as in Table D5 Sample Group B (Dalmatia, Slavonia, Crevalcore, Montegiorgio, Crete, Corfu)

VARIABLE	ACTIVITY CLASS	OCCUP CLASS	DECILES 1-7 O	DECILES 1-7 E	DECILES 8-10 O	DECILES 8-10 E
Relative Weight	1	Constant	238	264.1	225	198 9
" "	2	"	606	579.9	346	372 1
Relative Weight	Constant	1-13	114	155 5	158	116 5
" "	"	14-94	730	688 5	413	454 5
Σ Skinfolds	1	Constant	213	254 8	252	210 2
" "	2	"	599	557 2	343	384 8
Σ Skinfolds	Constant	1-13	102	138 1	156	119 9
" "	"	14-94	710	673 9	439	475 1
Systolic B P	1	Constant	291	302 7	172	160 3
" "	2	"	637	625 3	317	328 7
Systolic B P	Constant	1-13	171	176 0	101	96 0
" "	"	14-94	757	752 0	388	393 0
Diastolic B P	1	Constant	286	297 3	177	165 7
" "	2	"	639	627 7	320	331 3
Diastolic B P	Constant	1-13	163	175 5	111	98 5
" "	"	14-94	762	749 5	386	398 5
Serum Cholesterol	1	Constant	278	281 6	168	164 4
" "	2	"	600	596 4	332	335 6
Serum Cholesterol	Constant	1-13	153	162 7	104	94 3
" "	"	14-94	725	715 3	396	405 7

TABLE D8

Activity 1 vs Activity 2 Occupation Class constant Occupations 1-13 vs Occupations 14-94 Activity Class constant. O/E %" = numbers of men observed in deciles 8-10 as % of number expected Chi-square calculated from the 2 x 2 tables distributions observed and expected in deciles 1-7 and 8-10 "A" = East Finland West Finland Zutphen B' = Dalmatia Slavonia Crevalcore, Montegiorgio Crete Corfu

VARIABLE	ACTIVITY CLASS	OCCUPATION CLASS	SAMPLES	O/E %	CHI-SQUARE
Relative Weight	1	Constant	A	110 5	3 10
'	'	"	B	113 1	8 67
" '	Constant	1-13	A	137 3	26 43
' "	"		B	135 6	31 38
Σ Skinfolds	1	Constant	A	123 4	18 43
	'	'	B	119 9	22 30
'	Constant	1-13	A	135 0	28 62
" '		'	B	130 1	24 29
Systolic B P	1	Constant	A	103 7	n. s
"		'	B	107 3	n. s
	Constant	1-13	A	103 8	n s
	'	"	B	105 2	n. s
Diastolic B P	1	Constant	A	108 7	n. s
'		'	B	106 8	n. s
'	Constant	1-13	A	107 2	n. s
'			B	112 7	n. s
Serum Cholesterol	1	Constant	A	107 1	n. s
	'		B	102 2	n. s
	Constant	1-13	A	122 6	7 23
			B	110 3	n. s

ably greater than that achieved by the activity classification Neither classification is very powerful in segregating men with relatively high blood pressure For segregating high serum cholesterol the occupational classification tends to be more effective than the activity classification but the difference is small

Tables D6 D7 and D8 compared with Tables D3 show some of the extent to which differences in the distributions of high values of the variables attributed to physical activity are affected when account is taken of occupational status as well The relationship of physical activity *per se* to high values of the variables is obviously over-estimated in Tables D1—D3

Summary

The prevalence of specified high relative body weight and Σ skinfolds within samples is strongly related inversely to the estimated physical activity of the men in the sample Similar relationships but much less marked tend to hold for arterial blood pressure and for serum cholesterol concentration But it is necessary to allow for influences of socio-economic differences in estimating the influence of physical activity *per se*

Without regard to physical activity men may be classified into two broad socio-economic classes an upper class made up of professional men landowners executives important government officials etc and a lower class made up of all men in other occupations The upper class so defined contains men in Activity Class 1 (sedentary and light activity) and Class 2 (moderately active) but almost no men in Class 3 (heavy physical activity) This upper class of men shows a high concentration of relatively overweight and obese men and also tends to contain more men than expected with high blood pressure and high serum cholesterol values

When men matched in socio-economic class but differing in physical activity are compared (Activity Class 1 vs Class 2) the more sedentary men still tend to include undue numbers of men with high values of the measured variables but the apparent influence of physical activity is much less than when socio-economic class was ignored

When men matched in physical activity but differing in socio-economic status are compared the men in the upper class still tend to include undue numbers of men with high values of the measured variables but the apparent influence of socio-economic status is less than when physical activity is ignored

E ANTHROPOMETRIC INDICES AND SKELETAL FORM

Introduction

Various suggestions have been made about the possibility that susceptibility to coronary heart disease is related to the constitution" that is to say to body or skeletal type (cf e g Müller 1909 Catsch 1941 Kretschmer 1955) Classification systems and methods for measuring of appraising body type still are far short of any accepted standardization but there is a fair degree of agreement that coronary heart disease tends to be unduly common among men of the pyknic or athletic-pyknic types of Kretschmer (1955) i e the stocky sturdy type as contrasted with the lanky lean slight leptosomatic or asthenic type (or types)

Burkhardt (1939) concluded from pathological anatomic studies on 1232 cases that persons with the pyknic physique are inclined to early arteriosclerosis but that at older ages this difference in susceptibility tended to disappear Schettler (1961 p 128) reached a similar conclusion from materials collected at Basle and Marburg and Selberg (1951) reported that the development of aortic arteriosclerosis was some 20 years later among leptosomes than among *pyknics*

The problem of differentiating the influence of basic skeletal type from concomitant characteristics in regard to relative obesity is illustrated by the work of Böhle *et al* (1958) who reported a high dominance of the pyknic type among 321 men and 61 women with coronary heart disease and also noted that about half of the patients of both sexes were obese

In the United States most attention in regard to coronary heart disease has been given to the "somatotype" classification of Sheldon *et al* (1940) because of the influential study of Gertler and White (1954) on young men (under 40) with clinical coronary heart disease among whom the "endomorphic-mesomorph somatotype was much more common among the patients than among the control subjects Confirmation of these findings was provided by Spain *et al* (1953 1963) particularly in a large study on men aged 36—50 in New York, and by Paul *et al* (1963) in a follow-up study of industrial employees in Chicago

The endomorphic-mesomorph of Sheldon corresponds in some degree to the mixed pyknic-athletic type of Kretschmer a type that has been specially singled out as coronary-prone by Bähr (1938) and Linzbach (1959) Excessive frequency of coronary heart disease among well-built" athletic type of soldiers in *the British* army was commented on by Newman (1946)

Somatotyping in Sheldon s *system is*

ably greater than that achieved by the activity classification Neither classification is very powerful in segregating men with relatively high blood pressure For segregating high serum cholesterol the occupational classification tends to be more effective than the activity classification but the difference is small

Tables D6 D7 and D8 compared with Tables D3 show some of the extent to which differences in the distributions of high values of the variables attributed to physical activity are affected when account is taken of occupational status as well The relationship of physical activity *per se* to high values of the variables is obviously over-estimated in Tables D1—D3

Summary

The prevalence of specified high relative body weight and Σ skinfolds within samples is strongly related inversely to the estimated physical activity of the men in the sample Similar relationships but much less marked tend to hold for arterial blood pressure and for serum cholesterol concentration But it is necessary to allow for influences of socio-economic differences in estimating the influence of physical activity *per se*

Without regard to physical activity men may be classified into two broad socio-economic classes an upper class made up of professional men landowners executives important government officials etc and a lower class made up of all men in other occupations The upper class so defined contains men in Activity Class 1 (sedentary and light activity) and Class 2 (moderately active) but almost no men in Class 3 (heavy physical activity) This upper class of men shows a high concentration of relatively overweight and obese men and also tends to contain more men than expected with high blood pressure and high serum cholesterol values

When men matched in socio-economic class but differing in physical activity are compared (Activity Class 1 vs Class 2) the more sedentary men still tend to include undue numbers of men with high values of the measured variables but the apparent influence of physical activity is much less than when socio-economic class was ignored

When men matched in physical activity but differing in socio-economic status are compared the men in the upper class still tend to include undue numbers of men with high values of the measured variables but the apparent influence of socio-economic status is less than when physical activity is ignored

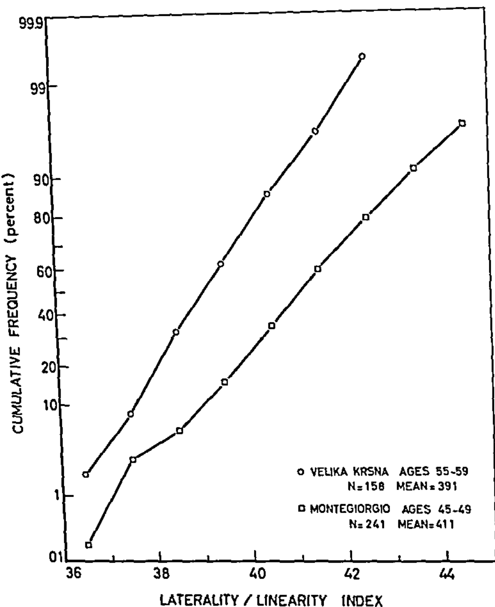

99.9
99
90
80
60
40
20
10
1
01
CUMULATIVE FREQUENCY (percent)
36
38
40
42
44
LATERALITY / LINEARITY INDEX
o VELIKA KRSNA AGES 55-59
N=158 MEAN=391
□ MONTEGIORGIO AGES 45-49
N=241 MEAN=411

Figure E1

a relatively subjective rating that appeared to be unsuitable for our cooperative research programs with different populations On the other hand a quantitative description of certain aspects of the body type can be provided by the anthropometric items covered in these studies — standing height, sitting height bi-acromial and bi-cristal diameters Relative body weight is, of course a crude mixture of influences of body type muscular development and body fat

The ratio of sitting to standing height is obviously a crude measure of relative *trunk plus head length* compared with leg length a high ratio suggests a stocky person or at least one aspect of stockiness Unfortunately, this ratio is not only determined by the skeletal components the thickness of the buttocks is included in the sitting height so the sitting height measurement of a steatopygous person will yield an erroneously high value for estimated trunk length

Another and perhaps better indication of the place in the stockiness-leanness continuum is the laterality-linearity index, defined as the ratio of the sum of the bi-acromial and bi-cristal diameters to the body length or standing height A high value for this index indicates a relatively broad skeletal framework

The masculinity-femininity continuum of skeletal type would seem to be accessible to appraisal by means of the ratio of the bi-acromial to the bi-cristal diameters a high index being the result of relatively wide shoulders and narrow hips and an indication of a more "masculine" type of skeleton

These three indexes plus relative body weight and the sum of the skinfolds by no means give a full and detailed picture of the "constitution' but it must be noted that in fact there is *no* agreement on what the "constitution" is supposed to be However these are quantitative variables objectively measured and their distributions in the several population groups and comparisons with other variables merit examination

Laterality-Linearity Index (L-L)

The laterality-linearity index (L-L) is the ratio of the sum of the bi-acromial and bi-cristal diameters to the total body length (standing height) This index proves to be normally distributed thus simplifying the presentation and analysis of the data Figure E1 gives two contrasting examples of the cumulative percentage frequency distribution plotted on a probability scale Besides showing normality of the distributions Figure E1 shows that the men of Montegiorgio and Velika Krsna differ the men aged 55—59 of Velika Krsna are more linear (the index is smaller) than the men aged 45—49 of Montegiorgio

Table E1 gives the means and standard deviations for the laterality-linearity index by 5-year age groups of the various samples of men With the exception of East Finland and Slavonia there is a general tendency for the values to rise slightly with age and this trend is significant in several of the samples (e g U S A Switchmen West Finland Montegiorgio Corfu) Such an age trend would be expected from a decrease of height with age with no change in the diameters of the girdles

As noted above the men of Velika Krsna differ significantly from those of Montegiorgio in being more linear in skeletal framework In general the most linear men are those of Velika Krsna and the railroad employees in the U S A while the most lateral men (relatively broad skeletal form) are those in Montegiorgio Crevalcore and Corfu the other populations being intermediate

Before accepting the reality of these indicated differences it is necessary to consider two questions of the technical measurement First it may be asked whether a relatively high value for the index may not be in part an artifact produced by inclusion of the skin and subcutaneous fat in the diameter measurements Though these tissues do contribute to the recorded diameters except in very obese men the sites chosen have only a relatively thin overlay of soft tissue and this is reduced still further by compression with the pelvimeter

The second question is whether slight differences in the technique of measurement of the diameters might be involved This seems most unlikely because the differences though small are much greater than variations observed in measurements made by different investigators with the same subjects A difference of 1 5 in the index as between 39 5 and 41 0 for example corresponds at equal height of 170 cm to a difference of 25 5 mm in the sum of the two diameters a value much greater than could be attributed to any ordinary differences in technique

In regard to possible relationships between the laterality-linearity index and susceptibility to coronary heart disease it is useful to explore the relationships between L-L and other variables that are believed to be associated with differences in susceptibility For example do men with high index values (relatively broad and stocky) tend to be unduly fat or to have elevated serum cholesterol values?

Table E2 summarizes the analysis of this question with regard to the sum of the skinfolds Men who have an index value L-L under 40 are classed as "linear" men with L-L = 41 or more are classed as "lateral" The distributions were obtained of "thin" and fat" men (in Σ skinfold decile classes 1 2 and 9 10 respectively) into these L-L classes The resulting 2×2 tables for each sample are condensed in Table E2 which also gives the chi square value calculated from each 2×2 table

In every case there is an excess of fat men (in the top 20 per cent of the distribution of sum of skinfolds for their age and sample) in the class of lateral men The probability of obtaining the observed distribution by chance is vanishingly small in all cases except Velika Krsna Hence it appears that men with wide skeletons tend to be represented with undue frequency among the fattest men while the men with narrow skeletons congregate among the thinnest men The result that emerges from this analysis is highly significant statistically and may also be biologically important On the other hand computation of the ordinary product-moment coefficient of correlation between these two variables produces small of negligible coefficients This does not necessarily mean that there is a real discrepancy in the two sets of results but it does emphasize the point discussed in Section B5 that serious errors may be produced by over-reliance on the product-moment coefficient of correlation when either of the variables concerned departs from a normal distribution or there is a non-linear relationship between the variables

The same approach as with L-L versus body fatness was used in the examination of the relationship between diastolic blood pressure and the laterality linearity index and the results are summarized in Table E3 In all samples there was an excess of the more lateral men in the top 20 per cent of the blood pressure distribution but this tendency was statistically significant within single samples only in the U S railway men in East Finland at Crevalcore Zutphen and Crete in the latter six samples p = less than 0 02 in every case For all samples considered together the average is an excess of 11 2

TABLF E1

Laterality-Linearity index mean values and standard deviations by 5-year age classes

GROUP	AGES							
	40-44		45-49		50-54		55-59	
	Mean	S D	Mean	S D	Mean	S D	Mean	S D
U S Switchmen	39 3	1 4	39 4	1 5	39 6	1 5	39 7	1 4
U S Sedentary Clerks	39 0	1 4	39 4	1 7	39 6	1 6	39 5	1 6
Dalmatia	39 7	1 3	40 2	1 4	40 1	1 3	40 2	1 4
Slavonia	40 6	1 5	40 8	1 4	40 7	1 7	40 7	1 5
East Finland	39 9	1 6	40 0	1 6	39 9	1 6	39 8	1 2
West Finland	39 6	1 4	39 6	1 5	40 0	1 5	40 1	1 6
Crevalcore	40 5	1 9	40 6	1 9	40 8	1 6	40 8	2 1
Montegiorgio	40 8	1 6	41 1	1 8	41 2	1 7	41 5	1 8
Zutphen	39 6	1 5	39 8	1 5	39 8	1 6	40 0	1 6
Crete	40 1	1 5	40 1	1 5	40 1	1 4	40 2	1 3
Corfu	40 3	1 7	40 4	1 6	40 7	1 9	40 8	1 5
Velika Krsna	38 8	1 4	39 3	1 3	39 3	1 3	39 1	1 4
Rome Railway Men	41 0	1 5	41 3	1 5	41 2	1 6	41 3	1 6
All Men (mean unweighted)	39 9	--	40 2	--	40 2	--	40 3	--

TABLE E2

Numbers of "LATERAL" (L-L = 41 or more) and "LINEAR" (L-L = under 40) men in the top (FAT) and bottom 20 per cent class of fatness (Σ skinfold decile classes 9 + 10 and 1 + 2 respectively) TOTAL N = number men in Σ skinfold decile classes 1 2 9 and 10

SAMPLE	TOTAL N		FAT LATERAL MEN		Chi^2
	LINEAR	LATERAL	OBSERVED	EXPECTED	
U S Switchmen	178	87	72	41 7	60 91
U S Sedentary Clerks	174	92	72	44 6	48 08
Dalmatia	90	99	67	50 8	20 90
Slavonia	50	161	94	83 2	11 20
Crevalcore	96	230	157	122 8	67 53
Montegiorgio	51	178	118	98 7	36 03
East Finland	118	123	89	63 8	40 59
West Finland	134	114	82	58 8	33 38
Zutphen	148	118	73	59 0	11 10
Crete	83	110	82	58 7	44 14
Corfu	50	108	67	56 1	12 80
Velika Krsna	127	28	17	12 8	2 37
Rome Railway Men	33	213	123	116 6	8 20
All Men	1332	1661	1113	853 5	363 3

per cent men with high blood pressure among the more lateral men and this deviation from chance expectation has the extraordinary value of chi square = 50.98. The conclusion is that, in general, hypertension tends to be more common among the men with skeletons of the more lateral type than among men with small values for L-L.

Finally this approach was applied to serum cholesterol concentration. The results are summarized in Table E4. The more lateral men tend to be represented with unexpectedly high frequency in the more hypercholesterolemic class of men in nine of the 13 samples but this trend is statistically significant only at Montegiorgio, Crete and Corfu. The trend among U. S. switchmen does not quite reach $p = 0.05$. For all samples combined there is a highly significant tendency for the more lateral men to have relatively high values for serum cholesterol.

Ratio of Sitting to Standing Height (S/S)

The ratio of sitting to standing height is normally distributed; two examples are given in Figure E2. Table E5 summarizes the data on 100 × the ratio of sitting to standing height (S/S) in the various population samples. Two points are clear in Table E5. In the first place, the variability of S/S is small, the standard deviation being only of the order of 2.5 per cent of the mean. Accordingly, even what at first sight may seem to be only trivial differences between mean values can be highly significant statistically when the numbers are fairly large, as they are in these samples.

The same methods were used in all samples and the same instructions about the technique of measurement were issued to all of the research teams, but it is impossible to insist that the values for S/S for the various samples are completely comparable. These height measurements seem to be so simple that it is difficult to persuade physicians and technicians about the great care needed in adjusting the posture to assure that the measurements are in fact always strictly comparable. However, within any one sample where the same observer made all of these measurements, the effect of variation and poor control of technique should merely increase the random error and comparisons between sub-samples should be valid.

For the present purposes, men with values of S/S = 54 or more are considered to be relatively "squatty," i.e., short-legged, while values of S/S = under 53 are relatively "lanky". It is of interest to ignore the men with intermediate values of S/S and to inquire how the characteristics of obesity, high blood pressure and high serum cholesterol concentration are distributed between the squatty and lanky men as defined here. The method used for this analysis is the same as used above in the analysis of laterality-linearity, i.e., attention is focussed on the bottom and top 20 per cent classes of the other variables considered.

Table E6 summarizes the results for the sum of the skinfolds. In all samples except Zutphen there is an excess of fat men in the squatty class and this is highly significant in most of the samples. For all samples combined there is an excess of 20.4 per cent of obese men in the squatty class and chi square has the extremely high value of 100.20. In part, of course, this result may be an artifact in that fat men (with thick skinfolds) may also have fat buttocks which in turn will contribute to their sitting height. It seems unlikely, however, that this can explain all of the association between squattiness and the sum of the skinfolds. The difference between S/S = 53 and S/S = 54 corresponds to a difference of 1.8 cm in sitting height when standing height =

TABLE E3

Numbers of "LATERAL" (L-L = 41 or more) and "LINEAR" (L-L = under 40) men in the top (HIGH B P) and bottom 20 per cent classes of diastolic blood pressure (deciles 9, 10 and 1, 2, respectively) Total N = number of men in diastolic B P decile classes 1, 2, 9 and 10

SAMPLE	TOTAL N		HIGH B P	LATERAL MEN	Chi^2
	Linear	Lateral	Observed	Expected	
U S Switchmen	169	77	48	38 5	6 13
U S Sedentary Clerks	180	84	53	42 3	7 24
Dalmatia	85	97	50	48 0	n s
Slavonia	48	155	87	81 7	2 54
Crevalcore	99	230	129	117 4	7 06
Montegiorgio	44	190	102	98 2	n s
East Finland	132	92	58	42 4	16 83
West Finland	130	120	65	57 6	3 06
Zutphen	145	119	72	60 4	7 54
Crete	86	101	61	50 8	8 15
Corfu	52	110	58	54 3	n s
Velika Krsna	123	32	17	16 9	n s
Rome Railroad Men	43	205	109	105 0	n s
All Men	1336	1612	909	812 0	50 98

TABLE E4

Numbers of "LATERAL" (L-L = 41 or more) and "LINEAR" (L-L = under 40) men in the top (HIGH CHOL) and bottom 20 per cent classes of serum cholesterol concentration (deciles 9, 10 and 1, 2, respectively) TOTAL N = number of men in cholesterol decile classes 1 2, 9 and 10

SAMPLE	TOTAL N		HIGH CHOL	LATERAL MEN	Chi^2
	Linear	Lateral	Observed	Expected	
U S Switchmen	168	76	46	38 9	3 30
U S Sedentary Clerks	179	76	38	37 0	n s
Dalmatia	91	98	50	47 2	n s
Slavonia	54	157	75	78 1	n s
Crevalcore	99	211	112	105 5	2 14
Montegiorgio	43	186	109	97 5	13 91
East Finland	132	89	42	43 1	n s
West Finland	81	153	78	79 1	n s
Zutphen	139	108	47	50 3	n s
Crete	76	101	63	52 5	9 24
Corfu	52	97	57	51 4	3 05
Velika Krsna	121	32	20	16 7	n s
Rome Railway Men	37	210	117	115 6	n s
All Men	1272	1594	854	806 5	12 52

TABLE E5

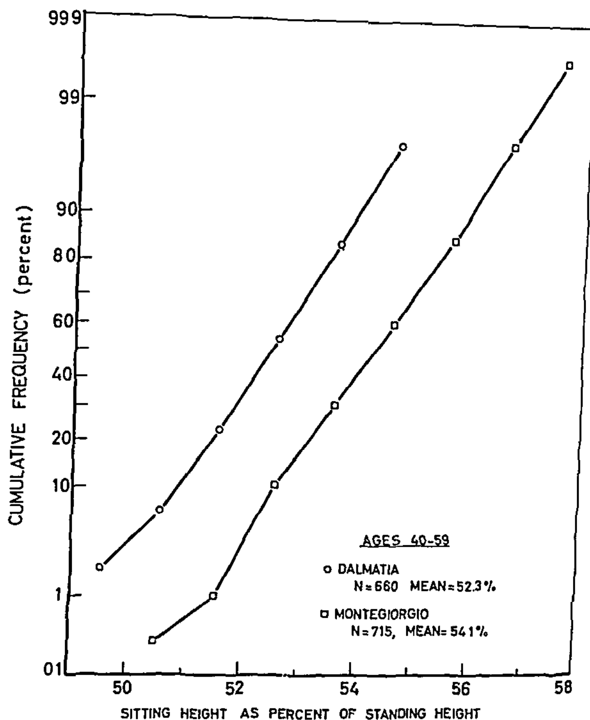
Sitting height as per cent of standing height mean values and standard deviation by 5 year age classes

SAMPLE	AGES 40 44 Mean	S D	45-49 Mean	S D	50 54 Mean	S D	55 59 Mean	S D
U S Switchmen	52 8	1 39	52 7	1 32	52 5	1 35	52 6	1 11
U S Sedentary Clerks	52 5	1 26	52 6	1 29	52 6	1 27	52 4	1 28
Tanushimaru	54 6	1 40	54 5	1 37	54 6	1 66	54 6	1 36
Dalmatia	52 3	1 18	52 2	1 37	52 3	1 32	52 4	1 20
Slavonia	52 5	1 17	52 5	1 39	52 5	1 35	52 3	1 30
East Finland	52 3	1 40	53 6	1 39	53 3	1 48	53 2	1 41
West Finland	52 8	1 37	52 9	1 24	52 6	1 41	52 5	1 41
Crevalcore	52 9	1 48	52 7	1 37	52 6	1 35	52 7	1 46
Montegiorgio	54 3	1 24	54 2	1 28	54 0	1 35	54 0	1 28
Zutphen	52 7	1 42	52 7	1 30	52 4	1 37	52 4	1 24
Crete	53 6	1 40	53 4	1 51	53 0	1 54	52 9	1 33
Corfu	53 1	1 23	52 7	1 45	52 9	1 38	52 9	1 35
Velika Krsna	52 5	1 29	52 5	1 28	52 4	1 21	52 4	1 48
Rome Railway men	53 7	1 42	53 6	1 36	53 5	1 42	53 6	1 22
Mean all men (unweighted)	53 04	-	53 06		52 94	-	52 92	--

TABLE E6

Numbers of SQUATTY' (S/S = 54 or more) and 'LANKY (S/S = under 53) men in the top (FAT) and bottom 20 per cent age specific Σ skinfold classes (deciles 1 2 and 9 10 respectively) Total N = men in Σ skinfold decile classes 1 2 9 and 10

SAMPLE	TOTAL N Lanky	Squatty	FAT SQUATTY MEN Observed	Expected	100(O/E)	Chi²
U S Switchmen	175	86	59	43 5	135 6	15 61
U S Sed Clerks	168	73	46	35 1	131 1	8 40
Dalmatia	139	39	31	20 2	153 5	14 02
Slavonia	148	51	32	25 1	127 5	4 32
Crevalcore	171	93	58	44 7	129 8	10 90
Montegiorgio	33	189	118	105 6	111 7	21 39
East Finland	76	148	82	78 0	105 1	n s
West Finland	140	102	62	53 5	115 9	4 35
Zutphen	164	84	40	40 6	98 5	n s
Crete	60	126	76	65 7	115 7	9 47
Corfu	77	86	57	42 7	133 5	18 75
Velika Krsna	104	47	29	22 7	127 8	4 16
Rome Railroad Men	53	150	90	81 3	110 7	6 92
All Men	1508	1274	780	648 0	120 4	100 20



99.9
99
90
80
60
40
20
10
1
0.1
CUMULATIVE FREQUENCY (percent)
50
52
54
56
58
SITTING HEIGHT AS PERCENT OF STANDING HEIGHT
AGES 40-59
o DALMATIA
N = 660 MEAN = 52.3 %
□ MONTEGIORGIO
N = 715, MEAN = 54.1 %

Figure E2

TABLE E7

Numbers of SQUATTY" (S/S = 54 or more) and LANKY (S/S = under 53) men in the top (HIGH B P) and bottom 20 per cent age-specific diastolic blood pressure classes (deciles 1 2 and 9 10, respectively) Total N = men in diastolic B P decile classes 1 2 9 and 10

SAMPLE	TOTAL N		HIGH B P SQUATTY MEN			Chi^2
	Lanky	Squatty	Observed	Expected	100(O/E)	
U S Switchman	175	87	52	44 2	117 6	3 67
U S Sed Clerks	170	72	42	37 5	112 0	n s
Dalmatia	143	51	27	27 3	99 0	n s
Slavonia	143	53	26	26 0	100 0	n s
Crevalcore	157	113	63	57 8	109 0	n s
Montegiorgio	33	200	109	104 7	104 1	n s
East Finland	69	158	81	83 5	97 0	n s
West Finland	129	111	65	55 5	117 1	5 43
Zutphen	166	76	45	36 4	123 6	3 55
Crete	73	120	64	61 6	103 9	n s
Corfu	73	67	36	33 0	109 1	n s
Velika Krsna	111	35	18	18 0	100 0	n s
Rome Railroad Men	51	159	75	73 4	102 2	n s
All Men	1493	1302	703	659 2	106 6	10 81

TABLE E8

Numbers of SQUATTY (S/S 54 or more) and LANKY (S/S = under 53) men in the top (HIGH CHOL) and bottom 20 per cent age specific serum cholesterol classes (deciles 1 2 and 9 10 respectively) Total N - men in serum cholesterol decile classes 1 2 9 and 10

SAMPLE	TOTAL N		HIGH CHOL SQUATTY MEN			Chi^2
	Lanky	Squatty	Observed	Expected	100(O/E)	
U S Switchmen	172	81	50	41 6	120 2	4 54
U S Sed Clerks	158	84	39	42 7	91 3	n s
Dalmatia	148	38	22	19 8	111 1	n s
Slavonia	136	48	28	21 1	132 7	4 69
Crevalcore	166	93	51	49 6	102 8	n s
Montegiorgio	26	171	98	94 6	103 6	n s
East Finland	76	152	77	75 3	102 3	n s
West Finland	135	107	54	54 4	99 3	n s
Zutphen	158	82	46	39 0	117 9	3 14
Crete	62	115	65	56 5	115 0	6 36
Corfu	71	70	38	35 2	108 0	n s
Velika Krsna	04	38	20	18 7	107 0	n s
Rome Railroad Men	49	155	84	99 8	105 3	n s
All Men	1461	1234	672	623 2	107 8	13 96

170 cm and a contribution of 1 8 cm of buttocks fat to the sitting height must be rare We conclude then that men with the squatty type of skeletal constitution are inclined to be fatter than their lanky counterparts

No such question of a possible artifact exaggerating the true relationship is raised in connection with diastolic blood pressure as summarized in Table E7 In 9 out of 13 samples the squatty men have an undue frequency of relatively high blood pressure and in 3 of these the tendency approaches or actually is significant For all samples considered together the squatty men include an excess of 6 6 per cent cases of relatively high blood pressure and this is statistically highly significant (p = about 0 001)

Finally Table E8 is concerned with S/S vs high values for serum cholesterol In 10 out of 13 samples the squatty men show an unexpected excess of men in the top 20 per cent of the age- and area-specific serum cholesterol distribution and this tendency is statistically significant in 3 of the samples For all samples considered together the excess of high cholesterol cases among squatty men averages 7 8 per cent and this is significant at p = less than 0 001

Bi-Acromial/Bi-Cristal Diameters, A/C

As indicated earlier the ratio of the bi-acromial to the bi-cristal diameter A/C may be considered to be some kind of an indication of the relative masculinity-femininity of the skeleton Accordingly it seemed to be desirable to examine the relationship if any between A/C and other variables of interest in connection with the tendency to coronary heart disease The distribution of A/C is such that it was decided to concentrate on values of A/C = 1 34 and over and A/C = under 1 28 these being relatively "tapered" and "straight", or "masculine' and "feminine' respectively The ratio A/C is generally distributed normally three examples are shown in Figure E3

The distributions of men with these values for A/C into the bottom and top (deciles 1 2 and 9 10) 20 per cent classes for Σ skinfolds diastolic blood pressure and serum cholesterol were determined for each of 13 samples no significant results were obtained for any sample except in the Rome railroad employees

In the Rome sample 38 men with A/C of 1 34 or more were in deciles 9 10 for Σ skinfolds but the chance expectation would be 53 2 men (chi-square = 17 28 p = less than 0 001) so it is concluded that in Rome there was a shortage of fat men in this more "masculine" grouping Also in the Rome sample the men with A/C of 1.34 or more included fewer cases (45) than expected (55 5) of relatively high diastolic blood pressure (chi-square = 8 13 p = less than 0 01) But when all samples are considered together there were no significant differences between these extreme classes of A/C in regard to observed vs expected frequency of high values of Σ skinfolds diastolic blood pressure or serum cholesterol

Laterality-Linearity and ECG Abnormalities

Possible relationships between laterality-linearity index L-L and the frequency of electrocardiographic abnormalities were sought by constructing two-by-two tables for L-L vs each of five ECG abnormalities for each of 13 samples of men For all 13 samples considered together among the more lateral men a total of 151 cases of left axis deviation (Code II 1) were observed but only 136 3 cases was the chance ex-

pectation (chi-square = 7 54 p = less than 0 01) Similarly among all the more lateral men there were 229 cases of high R wave left type (Code III 1) but 263 0 would be expected (chi-square = 20 49 p = less than 0 001)

In the individual samples the analysis was generally unrewarding except that slightly fewer cases of S-T depression were observed than expected in Zutphen and slightly more than expected in Crete (11 observed 16 4 expected chi-square = 3 07 in Zutphen 9 observed 5 1 expected chi square = 5 40 in Crete)

The Skinfold Thickness

The detailed data on the distributions of the skinfold thickness (Σ skinfolds) given in the Appendix show that this variable has almost no age trend from age 40—44 to 55—59 years in any of the population samples The only qualification to this conclusion is that there is a trivial tendency for the skinfolds to be thinnest in the oldest (55—59) men this is indicated in Table E9 Such tendency as there is to become thinner with age was most pronounced in Crete where in successive 5-year age groups the 90th centile cutting points for the sum of the skinfolds are respectively 38 28 27 and 23 mm The corresponding 90th centile points for the triceps skinfold in Crete are 13 14 11 and 9 mm

In the analyses in the present study we have used the sum of the two skinfolds that over the triceps and that over the tip of the scapula ('Σ skinfolds) as the measure of body fatness This is a better measure than any single skinfold though both the triceps and the scapula values are very highly correlated with Σ skinfolds

In some other studies skinfold thickness at other sites is reported but in most studies at least the triceps value is measured To allow comparison with such other studies the full distributions of the triceps skinfold thickness for each sample and age are given in the Appendix

Table E9 also shows that on the average the skinfold over the triceps muscle tends to represent a constant fraction of Σ skinfolds with no significant age trend At the median level the triceps skinfold averages 40 5 per cent of Σ skinfolds at the 90th centile the corresponding average is 42 8 per cent In other words in the fattest men the triceps tends to represent a trifle more of Σ skinfolds than in men in the middle of the distribution

Summary

Men with a relatively wide skeletal framework judged from the ratio of the sum of the bi-acromial and bi-cristal diameters to the total height (L-L) were found to have unexpectedly high tendencies to obesity high diastolic blood pressure and high serum cholesterol

In the electrocardiograms the more lateral men tended to show an excessive number of left axis deviations and a deficit of cases of high R waves left type

'Squatty" men (high values of the ratio of sitting to standing height S/S) were also found to include unduly high numbers of obese men and men with high values for diastolic blood pressure and serum cholesterol

The ratio of the bi-acromial to the bi-cristal diameter (A/C) is suggested as a kind of indicator of relative masculinity-femininity of the skeleton This measure was not found to be related to the frequency of high values for diastolic blood pressure or serum cholesterol There was a slight deficit (4 1 per cent) of obese men (deciles 9 10 in Σ skinfolds) among the men with high values of A/C

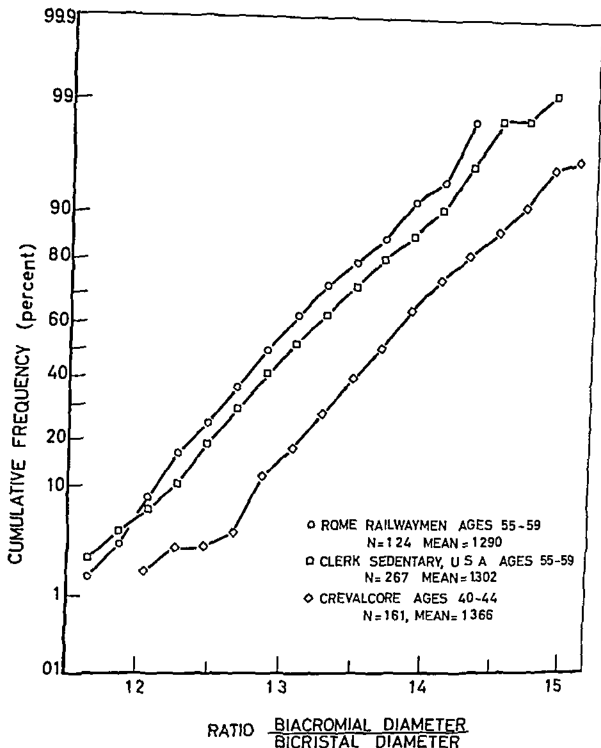

99.9
99
90
80
60
40
20
10
1
01
CUMULATIVE FREQUENCY (percent)
12
13
14
15
RATIO BIACROMIAL DIAMETER / BICRISTAL DIAMETER
ROME RAILWAYMEN AGES 55-59
N=124 MEAN=1290
CLERK SEDENTARY, U S A AGES 55-59
N=267 MEAN=1302
CREVALCORE AGES 40-44
N=161, MEAN=1366

Figure E3

Σ skinfolds shows almost no age trend from 40—44 to 55—59 except for a trivial tendency to be minimal in the oldest men The skinfold over the triceps muscle also shows no significant age trend and at all ages tends to represent a constant fraction of Σ skinfolds

TABLE E9

Skinfold thickness, trend with age Unweighted averages of the medians and of the 90th centile cutting points of 15 samples comprising 10 103 men

ITEM	MEDIANS				90TH CENTILES			
	40-44	45-49	50-54	55-59	40-44	45-49	50-54	55-59
No of men	2079	2729	2805	2490	2079	2729	2805	2490
Triceps	9 00	8 40	8 67	8 40	15 67	15 40	15 33	14 80
Scapula	12 61	12 81	13 01	12 28	20 61	20 48	20 55	20 15
Σ Skinfolds	21 61	21 21	21 68	20 68	36 28	35 88	35 88	34 95
Triceps as % of Σ Skinfolds	41 6	39 6	40 0	40 6	43 2	42 9	42 7	42 3

case in other populations (Blackburn *et al* 1962)

The data on smoking habits in the present series of studies may be helpful in indicating the extent to which interrelationships between smoking habits and other variables are universal and not merely associations in a common culture Some information about smoking habits was given for each sample separately in Section C above The present section deals with comparisons *among samples* and with the detailed analyses of relationships between smoking habits and other variables that are more suitable considered with the smoking data from all the samples at the same time

Comparison of the Samples

Table F1 summarizes the cigarette smoking habits of the men in 15 samples The highest frequency of non-smokers as well as of men who never smoked regularly is at Velika Krsna the lowest frequency of non-smokers is in the fishermen of Ushibuka but the smallest proportion of men who never smoked cigarettes is at Zutphen At the other extreme men who always smoke at least 20 cigarettes a day are most common in the two Japanese samples at Tanushimaru 42 1 per cent of the men 40—59 years old are in this heavy smoking category The lowest percentages of heavy cigarette smokers are at Montegiorgio and Zutphen

Zutphen is alone among these populations in having a high frequency of cigar and pipe smoking men who smoke both cigarettes and cigars or pipes are common there, as elsewhere in the Netherlands but in none of the other sample areas It is interesting too that at one time at least 92 4 per cent of the men of Zutphen had been regular cigarette smokers and at the time of this study there were more light smokers (of cigarettes) than in any other sample

The statistical significance of the differences between samples in cigarette smoking habits has been tested by chi-square applied to the data in 2X2 tables of the numbers of non-smokers versus those of the regular smokers (10 or more cigarettes every day) The more interesting results of the chi-square test are given in Table F2

In smoking habits expressed in this way there is no significant difference between U S railroad switchmen and Rome railroad employees but the Rome railroad men clearly smoke more than the U S railroad clerks The Rome railroad men smoke more than men in the other Italian samples i e. those in Crevalcore and Montegiorgio Though the men in Dalmatia do not differ in this respect from those in Slavonia, the men in both of these areas of Croatia smoke more than the men of Velika Krsna In Finland too there is a real difference between the samples the East Finland (Karelia) men smoking more than the men of West Finland but in part this difference may reflect the fact that the use of the Russian type of cigarette (paperossi) which contains much less tobacco is fairly common in Karelia

Consideration of the frequency of heavy smoking (20 or more cigarettes daily) changes the general picture little but a few details are altered The relatively high frequency of heavy smoking in Crete (29 6 per cent) puts the men in that sample in a heavier smoking category than the men in Corfu (chi-square = 9 85 or Dalmatia (chi-square = 8.39) In respect to such heavy cigarette smoking the men of Tanushimaru prove to be insignificantly different from the men of Ushibuka

Perhaps the most striking feature of these comparisons is the similarity of the smoking habits of these populations that have so many cultural differences

F SMOKING HABITS

A major by-product of investigations on the relation of lung cancer to smoking has been the finding in certain populations that the death rate ascribed to coronary heart disease is related to the habit of smoking cigarettes (Doll and Hill 1956 Hammond and Horn 1958) This finding has been confirmed in prospective (follow-up) studies in the U S A directed primarily at coronary heart disease (Doyle *et al* 1962)

In the present-day cultural setting of the U S A and Great Britain men who smoke cigarettes are more prone to have heart attacks and to die of coronary heart disease than their contemporaries who do not smoke and the risk increases with the number of cigarettes smoked daily But this increased risk has not been shown to extend to men who smoke only pipes or cigars Moreover coronary heart disease is not unduly frequent in *all* populations that are characterized by heavy cigarette smoking (Keys 1962) These and other reasons suggest that cigarette smoking itself may not be a direct factor in the etiology of the disease the tendency to smoke cigarettes may be associated with other characteristics of the person and his mode of life more directly responsible for increased susceptibility to this disease It is entirely possible that the kind of person who is inclined to be a heavy cigarette smoker would also be prone to coronary heart disease even if he did not smoke

Elsewhere we have noted that some of the peculiarities in the reported relationship of coronary heart disease susceptibility to smoking habits might be explained on the hypothesis that cigarette smoking is particularly baleful in populations subsisting on high-fat diets and whose blood cholesterol levels are correspondingly elevated (Keys and Blackburn 1963) Even if cigarette smoking does not promote atherogenesis it is conceivable that smoking might trigger the clinical event perhaps by causing arrhythmias in the sensitive situation where the coronary arteries are already seriously diseased

Previous studies have reported interesting but not always consistent differences between smokers and nonsmokers Thomas (1958 1960) found that heavy-smoking medical students are more often overweight than their fellows who smoke little or not at all but the reverse is true among middle-aged men in Finland (Karvonen *et al* 1959) and in the U S A (Blackburn *et al* 1962) Again heavy cigarette smokers have been reported to have a tendency to higher serum cholesterol levels than their non-smoking counterparts in some populations (Karvonen *et al* 1959 Thomas 1960 Bronte-Stewart *et al* 1960) but this may not be the

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Except for Montegiorgio and Ushibuka at the two extremes the percentage of regular (10 or more daily) cigarette smokers varies only from 39 to 59 per cent

Some of the differences in smoking habits are certainly ascribable in part to economic rather than cultural or innate psychological factors Cigarettes are much cheaper in Japan Greece and Yugoslavia than in Italy where heavy cigarette smoking is a formidable expense for such farmers as those at Montegiorgio who have a very small cash income

Non Smokers

Non-smokers comprise men who never smoked at least never smoked regularly and those who smoked for a time and then stopped Conceivably these two kinds of non-smokers might differ in respect to one or more of the variables of present concern so before pooling them for later comparison with the smokers this question was examined For each of the samples the men who never smoked were compared with the stopped smokers by examining the respective distributions above and below the median (for all men in the same 5-year age group in the same sample) for each of the five variables — relative weight sum of skinfolds systolic and diastolic blood pressure and serum cholesterol concentration Test by chi-square failed to show a single significant ($p = 0.05$) difference in any of the 60 sets of comparisons It was concluded therefore that it would be justifiable to pool all non smokers of each sample in further analyses

Cigarette Smoking and Physical Activity

Before examining possible relationships between cigarette smoking habits and other variables it is desirable to determine whether in such analyses it is necessary to separate the men according to physical activity For this purpose the distribution of men classed by smoking habits and by physical activity was determined for the various samples In none of these samples was there a significant difference in the distribution of smoking habits among sedentary and light activity men as compared with the men of the same age in the same area who customarily engaged in heavy physical activity

The data for all the samples may be illustrated by Table F3 which covers one sample each from Yugoslavia Finland Italy and Greece In this table the comparison is made between confirmed non-smokers (men who never smoked or have long stopped) and men who always smoke 10 or more cigarettes a day There is nothing like a consistent trend and the departures of the observed (O) from the expected (E) numbers do not approach statistical significance

Relative Body Weight and Fatness

Table F4 summarizes the distribution of the men classed by smoking habits into LOW (deciles 1—3) and HIGH (deciles 8—10) values for relative body weight If relative body weight were unrelated to smoking habits among all men in any given smoking category about 30 per cent would be expected to be in the LOW weight class and an equal number in the HIGH weight class

It is obvious from Table F4 that the distribution observed does not conform to chance expectation In every sample there are more non-smokers in the HIGH than in the LOW weight class The discrepancy is very large indeed except for Tanushimaru where the proportion of HIGH to LOW is only 1 15

TABLE F1

Cigarette smoking habits of men 40-59 in 15 samples Percentages of the men who NEVER smoked regularly, who are NON-SMOKERS (never + quit) LIGHT smokers (less than 10 daily) REGULAR (10 or more cigarettes daily) or HEAVY (20 or more daily), and the smoking RATIO (ratio of regular to non-smokers)

SAMPLE	TOTAL N	NEVER %	NON %	LIGHT %	REGULAR %	HEAVY %	RATIO
U S Clerks	858	27 2	47 9	6 2	45 7	16 4	0 96
U S Switchmen	836	16 4	35 2	5 6	59 2	30 1	1 68
Dalmatia	668	29 8	41 3	7 4	51 3	22 6	1 24
Slavonia	694	26 5	41 5	9 5	51 0	18 9	1 28
East Finland	815	19 5	31 5	10 1	58 4	31 4	1 83
West Finland	855	24 3	42 2	15 5	42 3	14 8	1 02
Crevalcore	987	25 1	36 3	19 5	44 2	17 7	1 18
Montegiorgio	714	25 9	41 2	27 7	31 1	9 5	0 76
Zutphen	869	7 6	25 6	30 2	44 2	10 7	1 75
Crete	685	23 6	42 6	10 3	47 1	29 6	1 10
Corfu	529	24 4	36 5	13 3	50 2	21 7	1 38
Velika Krsna	508	41 0	51 8	9 4	38 8	13 6	0 75
Tanushimaru	509	15 7	31 7	10 6	57 7	42 1	2 12
Ushibuka	494	15 0	22 3	8 2	69 5	37 4	3 12
Rome Railroad Men	765	18 7	34 8	10 8	54 4	29 9	1 56

TABLE F2

Significance of differences between samples in cigarette smoking habits indicated by the distribution of men into the classes non-smokers and smokers (10 or more cigarettes daily) The sample with the greater smoking habit is indicated by full capitals The probability of chance explanation is given under the heading p

COMPARISON	Chi-square	p
DALMATIA vs Slavonia	0 11	non-sig
U S SWITCHMEN vs Rome Railroad Men	0 39	" "
ROME RAILROAD MEN vs U S Clerks	23 36	Less than 0 001
ROME RAILROAD MEN vs Crevalcore	7 03	" " 0 01
ROME RAILROAD MEN vs Montegiorgio	36 47	" " 0 001
U S SWITCHMEN vs U S Clerks	32 27	" " 0 001
CORFU vs Crete	6 59	" " 0 02
USHIBUKA vs Tanushimaru	5 39	" " 0 03
DALMATIA vs Velika Krsna	15 58	" " 0 001
SLAVONIA vs Velika Krsna	23 13	" " 0 001
CREVALCORE vs Montegiorgio	14 47	" " 0 001
EAST FINLAND vs West Finland	30 56	" " 0 001

to 1 00 The reverse situation prevails among the "moderate" (10—19 cigarettes daily) and the "heavy" (20 or more daily) smokers the moderate smokers particularly are more often relatively underweight than overweight The "light" (less than 10 cigarettes daily) smokers show no consistent trend in regard to relative body weight

Table F5 summarizes in the same way the distribution of the thinnest and the fattest men i e the men in deciles 1—3 and 8—10 for skinfold thickness The picture is similar to that for relative body weight obesity is unduly common among the non smokers moderate smokers include an undue proportion of the thinnest men

Among urban men in the U S A a direct effect of smoking on relative weight and obesity is indicated from observations on persons who stop smoking after cultivating the habit for many years (Brozek and Keys 1957) In most cases there is a gain in body weight and very often a real problem of obesity control arises Recently stopped smokers often are inclined to eat candy or take between meal snacks though they never did this previously when they were smoking It could be suggested that the weight gain after stopping smoking may result from a substitute of a new eating habit for the former habit of smoking This explanation does not suffice for the findings in the present surveys because there is no difference in the distribution of relative weight or fatness between men who never smoked and those who smoked and then stopped A direct effect of smoking on appetite seems to be a reasonable explanation

Arterial Blood Pressure

The relationship between blood pressure and smoking habits has been analyzed in the same way as was done with relative body weight i e attention was concentrated on the distribution of the 30 per cent of the men with the highest blood pressure as contrasted with the 30 per cent of the men with the lowest blood pressure values Tables F6 and F7 summarize the findings for systolic and diastolic blood pressure respectively

Non-smokers tend to include an undue proportion of men with relatively high systolic blood pressure this was seen in all samples except Zutphen Tanushimaru and U S Railroad Clerks For the entire material combined the excess of men with relatively high blood pressure among the non-smokers surpasses chance expectation with very high statistical significance The largest number of decile 8—10 men expected among the non-smokers at the upper limit of $p = 0\ 01$ would be 1 277 while 1 372 was the number actually observed

Among light smokers (less than 10 cigarettes per day) there is no consistent trend in regard to the frequency of high or low systolic blood pressures In 6 samples there is a statistically significant excess of high blood pressure men in this class but there is an equally significant shortage of high systolic blood pressure men among the light smokers in West Finland and Crevalcore For all light smokers combined the systolic blood pressure distribution is very close to chance expectation

The excess of high systolic blood pressure among non-smokers is reflected in a corresponding shortage of men with such high values among the "regular smokers i e those men who always smoke 10 or more cigarettes a day The samples of men of Zutphen and Tanushimaru are again exceptional in not exhibiting the trend that is so clear among the men in the other samples

The diastolic blood pressure distributions summarized in Table F7 show the same trends as observed in regard

TABLE F3

Distribution according to cigarette smoking habits of men classified by habitual level of physical activity in 4 representative samples O = number of men observed, E = expected Chi-square values calculated with Yates' correction

	SMOKING	ACT 1 + 2		ACTIVITY 3	
		O	E	O	E
SLAVONIA	Never + Quit	77	69 0	199	207 0
	10 or more/day	86	94 0	288	280 0
	Chi-square = 1 96				
EAST FINLAND	Never + Quit	77	72 4	177	181 6
	10 or more/day	128	132 6	337	332 4
	Chi-square = 0 85				
MONTEGIORGIO	Never + Quit	95	104 0	198	189 0
	10 or more/day	87	78 0	135	144 0
	Chi-square = 2 55				
CORFU	Never + Quit	141	132 4	51	59 6
	10 or more/day	174	182 6	91	82 4
	Chi-square = 2 91				

TABLE F4

S[illegible]ing and relative body weight Numbers of men classed by cigarette smoking ha[illegible]s with LOW (deciles 1-3) and HIGH (deciles 8-10) values for relative body [illegible] "LIGHT" - 1-9 daily "MODERATE" = 10-19 "HEAVY" - 20 or more

SA[illegible]	NEVER + QUIT		LIGHT		MODERATE		HEAVY	
	LOW	*HIGH*	*LOW*	*HIGH*	*LOW*	*HIGH*	*LOW*	*HIGH*
U S Clerks	95	150	16	15	103	53	44	38
U S Switchmen	49	117	11	20	95	47	95	66
Dalmatia	61	107	12	14	73	39	54	37
Slavonia	35	190	22	20	96	34	56	24
East Finland	51	109	24	29	88	33	76	67
West Finland	65	152	43	27	95	40	46	30
Crevalcore	60	139	53	53	122	51	55	51
Montegiorgio	63	119	69	46	66	33	27	15
Zutphen	52	85	83	64	98	73	26	37
Crete	55	111	18	22	51	23	79	46
Corfu	31	82	18	26	61	27	48	23
Velika Kr[illegible]na	65	96	20	9	48	28	17	19
Tanushimaru	46	53	4	3	39	37	63	59
Ushibuka	22	42	13	5	64	31	47	58
Rome Railroad Men	47	109	17	30	59	43	104	48
TOTAL	797	1661	422	383	1158	592	837	618

TABLE F7

Smoking and diastolic blood pressure Numbers of men classed by cigarette smoking habits with LOW (deciles 1-3) and HIGH (deciles 8-10) values for diastolic blood pressure 'LIGHT" = 1-9 daily 'MODERATE" = 10-19 "HEAVY' = 20 or more

SAMPLE	NEVER + QUIT		LIGHT		MODERATE		HEAVY	
	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH
U S Clerks	117	126	14	20	86	49	40	42
U S Switchmen	75	97	12	16	96	69	68	69
Dalmatia	69	100	10	16	65	43	55	41
Slavonia	60	104	18	22	77	47	53	35
East Finland	50	88	27	28	81	56	84	70
West Finland	79	142	46	20	79	59	52	35
Crevalcore	82	141	46	59	100	48	64	46
Montegiorgio	85	95	57	58	51	37	22	24
Zutphen	53	81	85	71	98	74	27	32
Crete	75	104	18	23	41	33	69	43
Corfu	40	75	21	21	59	37	39	26
Velika Krsna	78	86	13	12	44	30	17	25
Tanushimaru	44	42	6	0	40	42	63	69
Ushibuka	22	47	15	7	55	41	55	54
Rome Railroad Men	58	99	22	28	66	43	83	59
TOTAL	987	1427	410	401	1038	708	791	670

TABLE F8

Smoking and serum cholesterol concentration Numbers of men classed by cigarette smoking habits with LOW (deciles 1-3) and HIGH (deciles 8-10) values for serum cholesterol LIGHT = 1-9 daily MODERATE" = 10-19 "HEAVY' = 20 or more

SAMPLE	NEVER + QUIT		LIGHT		MODERATE		HEAVY	
	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH
U S Clerks	129	123	16	16	68	80	43	36
U S Switchmen	82	81	16	13	66	73	83	80
Dalmatia	84	82	6	20	52	50	55	44
Slavonia	64	97	20	17	72	55	46	32
East Finland	80	74	27	28	60	66	78	77
West Finland	122	99	36	27	67	85	30	46
Crevalcore	106	113	65	40	81	68	36	67
Montegiorgio	71	93	72	48	49	48	21	24
Zutphen	67	66	77	61	87	84	17	36
Crete	82	99	22	19	35	26	57	52
Corfu	52	68	21	24	49	32	35	31
Velika Krsna	88	70	14	11	31	46	20	26
Tanushimaru	44	45	3	1	24	44	77	58
Ushibuka	31	33	17	10	41	51	58	54
Rome Railroad Men	83	85	32	20	58	58	55	65
TOTAL	1185	1228	444	355	840	866	711	728

TABLE F5

Smoking and body fatness Numbers of men classed by cigarette smoking habits, with LOW (deciles 1-3) and HIGH (deciles 8-10) values for sum of skinfold thickness "LIGHT" = 1-9 daily, "MODERATE" = 10-19 "HEAVY" = 20 or more

SAMPLE	NEVER + QUIT		LIGHT		MODERATE		HEAVY	
	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH
U S Clerks	104	142	12	16	94	57	48	44
U S Switchmen	56	114	16	20	96	50	83	65
Dalmatia	66	106	16	17	72	42	45	32
Slavonia	35	128	19	20	96	33	56	24
East Finland	44	109	28	21	84	92	89	60
West Finland	55	165	46	29	106	37	48	25
Crevalcore	69	137	58	58	112	49	56	51
Montegiorgio	57	123	70	55	63	30	25	17
Zutphen	48	90	82	65	106	65	23	39
Crete	57	124	16	17	54	27	78	38
Corfu	34	87	18	25	69	26	38	21
Velika Krsna	57	98	22	6	52	28	19	20
Tanushimaru	41	61	2	1	45	29	62	59
Ushibuka	-	-	-	-	-	-	-	-
Rome Railroad Men	46	97	17	36	63	44	101	59
TOTAL	769	1581	422	386	1112	609	771	554

TABLE F6

Smoking and systolic blood pressure Numbers of men classed by cigarette smoking habits with LOW (deciles 1-3) and HIGH (deciles 8-10) values for systolic blood pressure "LIGHT" = 1-9 daily "MODERATE" = 10-19 "HEAVY" = 20 or more

SAMPLE	NEVER + QUIT		LIGHT		MODERATE		HEAVY	
	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH
U S Clerks	131	127	9	20	77	70	40	40
U S Switchmen	75	101	11	13	94	66	71	71
Dalmatia	67	102	8	18	72	45	52	34
Slavonia	64	103	13	21	77	55	54	28
East Finland	75	86	26	27	67	68	74	61
West Finland	92	126	57	24	70	67	38	39
Crevalcore	87	122	60	49	91	64	54	60
Montegiorgio	81	89	53	62	56	41	23	23
Zutphen	67	66	81	77	86	81	29	35
Crete	75	103	17	26	47	31	64	43
Corfu	38	75	17	26	65	32	39	26
Velika Krsna	74	84	11	14	46	34	20	22
Tanushimaru	57	49	4	0	33	39	59	65
Ushibuka	22	41	12	9	56	48	58	51
Rome Railroad Men	76	98	25	26	63	47	64	60
TOTAL	1081	1372	404	412	1000	788	739	658

TABLE F9

Distribution of men with high values (deciles 9 10) for certain variables among heavy (20 or more daily) and regular (10-19 daily) cigarette smokers Tabulated values are numbers of heavy smokers expressed as % of chance expectation * p less than 0 05 ** p less than 0 01

MEN IN DECILES 9 AND 10 FOR

SAMPLE	RELATIVE WEIGHT	FATNESS	SYST B P	DIAST B P	CHOLES TEROL
U S Clerks	113 7	118 5	104 8	102 4	86 0
U S Switchmen	118 1	123 3**	115 7	111 0	96 1
Dalmatia	105 0	96 8	107 0	116 1	96 2
Slavonia	115 4	112 8	82 0	101 1	102 6
East Finland	127 6**	109 2	86 2	98 7	97 5
West Finland	118 8	125 0	98 0	101 0	107 8
Crevalcore	140 8**	126 0	118 8*	116 6	121 4**
Montegiorgio	136 8	136 9	115 9	114 3	119 2
Zutphen	129 7*	140 5*	106 2	136 8*	125 8
Crete	110 7	123 3	99 1	100 7	99 7
Corfu	121 2	123 8	105 7	104 1	109 3
Velika Krsna	115 8	124 7	130 5	132 8*	116 9
Tanushimaru	93 5	128 3**	102 9	99 3	83 5**
Ushibuka	121 9*	-	110 7	111 1	91 8
Rome Railroad Men	92 4	99 4	105 4	107 4	110 7

TABLE F10

Percentage excess of cases of relative systolic hypertension (top 3 deciles) among non smokers 1) ignoring relative obesity (ALL) and 2) omitting men in the top 3 deciles of Σ Skinfolds (NOT FAT) CHI SQUARE is calculated from numbers of smokers vs non smokers in decile classes 1 3 and 8 10 of systolic B P (one degree of freedom)

SAMPLE	% EXCESS HIGH B P ALL	% EXCESS HIGH B P NOT FAT	CHI SQUARE ALL	CHI SQUARE NOT FAT
U S Switchmen	12 9	8 8	3 97	0 76
Dalmatia	17 8	19 7	8 00	2 72
Slavonia	21 9	28 4	12 29	6 14
Crevalcore	16 2	17 6	8 13	4 15
Crete	12 1	14 4	3 99	1 81
Corfu	32 7	48 9	1 78	10 69
Rome Railroad Men	22 5	18 3	10 49	3 02
Ushibuka	20 8	26 1	1 13	0 91
All 8 Samples	18 4	19 1	60 17	25 25

to systolic blood pressure but the departures from random expectation are even more marked High diastolic blood pressure is unduly common among non-smokers, light smokers show no consistent trend one way or the other, while men with high diastolic blood pressure are underrepresented among the moderate and heavy cigarette smokers

Serum Cholesterol

Table F8 concerns serum cholesterol concentration There is no consistent pattern for all areas though certain areas show interesting pictures For example, in Slavonia there is a 21 per cent excess of high (deciles 8—10) cholesterol values among non-smokers as compared with men who smoke 10 or more cigarettes daily and this is highly significant ($p = 0\,001$) On the other hand in West Finland there is a 10 7 per cent *deficit* of high values for cholesterol among the non-smokers and this is also significant ($p = 0\,04$)

Degree of Smoking

It was observed that non-smokers tend to be heavier fatter and to have higher blood pressures than cigarette smokers But it does not follow that as smoking increases the men progressively tend to become lighter thinner and to have lower blood pressures Table F9 compares heavy smokers with moderate smokers (20 or more vs 10—19 cigarettes daily)

Compared with moderate smokers the heavy smokers tend to be in the top of the distribution (deciles 9 and 10) for relative weight (13 of 15 samples), body fatness (12 of 14 samples) systolic (11 of 15) and diastolic blood pressure (13 of 15 samples) In regard to these variables the moderate smokers would seem to have better characteristics than either non-smokers or heavy smokers This is shown for example, by computing the frequency of high blood pressure among each class of smokers expected as compared with observed on the basis of no difference between the classes of smokers When this calculation is made for systolic blood pressure in all samples combined the percentage difference between observed and expected frequency of hypertension proves to be +11.8 per cent for non-smokers +0 9 per cent for light smokers —11 1 per cent for moderate smokers and —5 1 per cent for heavy smokers

Arterial Pressure vs Fatness and Smoking

Non-smokers tend to be fatter than smokers so it may be asked whether the trend to higher blood pressures among non-smokers in most of the samples can be dependent on this tendency Cigarette smoking depresses the appetite thinner men tend to have lower-blood pressures — is this the explanation?

Some light can be thrown on this question by eliminating the fatter men from the analysis Table F10 shows for eight samples the percentage excess of cases of relative systolic hypertension (the top 3 deciles of the systolic blood pressure distribution) among non-smokers calculated from the number of cases observed and the number expected if non-smokers and smokers were alike

Ignoring relative obesity ("ALL") in every sample there is an excessive frequency of relative "hypertension" among the non-smokers ranging from 12 9 per cent among U S Switchmen to 32 7 per cent at Corfu the (unweighted) average being 19 6 per cent The chi-square values show that the excess has statistical significance in six of the samples When only relatively thin men are considered (deciles 1—7 in Σ skin-

"moderate" smokers (10—19 cigarettes daily) Light smokers (under 10 cigarettes daily) tended to have lower serum cholesterol values than their fellows in the same samples but otherwise serum cholesterol showed little or no relationship to smoking habits in most areas Exceptions were Slavonia Montegiorgio Crete and Corfu where nonsmokers tended to have high cholesterol values and Velika Krsna where the opposite tendency prevailed

In general smoking habits were unrelated to physical activity but did change somewhat with age the proportion of stopped smokers rising with increasing age. However among smokers the intensity of smoking did not change significantly with age over the range 40—59 years

The tendency for non-smokers to have higher blood pressures than the smokers could not be explained by the excess of obese men among the nonsmokers

folds) there is also an excessive number of cases of hypertension among the non-smokers ranging from 8 8 per cent among U S Switchmen to 48 9 per cent among men at Corfu the average being 22 8 per cent The chi-square values are smaller (except at Corfu) when the analysis is confined to thinner men but this is at least partly explained by the fact that the number of non-fat non-smokers is relatively small in most samples

The upshot of this analysis is to conclude that the tendency for non-smokers to have higher blood pressures than cigarette smokers is not explained by body fatness Either cigarette smoking tends to keep the blood pressure lower than it would be otherwise or non-smokers are simply the kind of men who more often tend to become hypertensive

Age and Smoking Habits

The prevalence of cigarette smoking in these samples falls with increasing age over the range 40—59 years in U S and Italian railroad workers in Dalmatia Zutphen and Crete and not in the other samples In those samples where the percentage of non-smokers increases with age this mainly reflects a rise in stopped smokers though in Dalmatia and Zutphen the percentage of never smokers also rises with age

The percentage of heavy smokers (20 or more daily) in these samples tends to fall with age except in Dalmatia Slavonia Nicotera Corfu and among U S clerks Among the men who do smoke in general the percentage of heavy smokers tends to remain constant i e the intensity of smoking does not change among those who continue to smoke but again there are exceptions Among smokers the percentage of heavy smokers tends to fall with age in East Finland Velika Krsna, Crevalcore Montegiorgio, Zutphen and in the U S clerks

The total picture in regard to age and smoking habits, then is that at ages 40—59 age is relatively unimportant except for a tendency for a few men to stop smoking and a few others to cut down from former heavy smoking

Summary

Except at Velika Krsna the majority of the men in all samples smoked cigarettes at the time of the examinations the highest prevalence being in Japan which also had the highest percentage of heavy smokers (20 or more cigarettes daily) At Velika Krsna 51 8 per cent were non-smokers and 41 0 per cent had never smoked regularly The highest percentage of stopped smokers was found in the U S railroad clerks (20 7 per cent) U S railroad switchmen smoked more than U S railroad clerks but no more than the Italian railroad employees

In none of the measured characteristics in any of the samples was there any significant difference between men who had stopped smoking and those who had never smoked but non-smokers consistently differed from smokers in being relatively heavier and fatter The non-smokers also tended to have higher blood pressures than the smokers except at Tanushimaru Japan, where there was no consistent difference between smokers and non-smokers though significant differences in one direction or the opposite were observed in several samples

For all samples considered together fewer heavy smokers were above than below the age- and area-specific median in relative body weight Σ skinfolds systolic and diastolic blood pressure but the lowest frequency of high values in these variables was found among the

between ECG findings and absolute levels of the physical measurement is not given but rather the relative standing within his population of a subject with a particular ECG abnormality

In Tables G1 through G5 the concentration of men with specified ECG findings is indicated by quintile classes from the lowest twenty per cent (quintile 1) to the highest twenty per cent of men (quintile 5) as well as the concentration of men above and below the group median

These ECG findings are usually too infrequent to attempt such analyses within single areas but the consistency of the trends may be inspected along with the relationships found for all areas pooled

Absence of a relationship between an ECG finding and a physical characteristic would be indicated by approximately equal numbers of cases in the Tables G 1—5 or equal proportions in the Figures G 1—5 within each quintile class of physical characteristic. There are approximately 5 130 men above and below the median cut for each physical variable and 2 052 in the base population for each quintile class

Q Waves (I 1)

The relationship of specified large Q waves widely considered to represent old myocardial infarction to five physical characteristics is shown by area in Table G1 and for 12 areas combined in Table G1 and Figure G1 A total of 74 of these "hard core" Q items occurred among 10 260 men aged 40—59 a prevalence of less than 1 per cent

The Q wave finding is concentrated among the thinner men (Σ skinfolds) (chi square quintile 1 vs 5 = 5 65 p < 025) and lighter men (RBW) (chi-square quintile 1 vs 5 = 10 12 p < 005) The differences are *statistically* significant between the upper and lower quintiles and the trend is consistent for all areas

A relationship of "infarct' Q waves to systolic blood pressure is apparent due to an excess of cases in the highest blood pressure quintile (chi-square quintile 1 vs 5 = 5 07 p < 025) A less distinct relationship exists with diastolic pressure where there is a paucity of Q wave cases in the lowest quintile and an excess in the highest (chi-square quintile 1 vs 5 = 4.35 p < 05) A similar and not very striking general relationship holds between the prevalence of ambulant infarct cases by ECG criteria and the serum cholesterol level "after the event" (chi-square quintile 1 vs 5 = 3 81 p = 05)

Left Axis Deviation (II 1)

The cut-off value for abnormal left axis deviation most often used clinically is —30 degrees a distinctly upward and leftward electrical orientation of the frontal plane QRS vector It is considered a "non-specific finding suggesting myocardial disease and here occurred in about 4 % of the total men of all populations

In Table G2 and Figure G2 "abnormal left axis deviation has little association with the other physical characteristics and no statistically significant differences occur

High Amplitude R Waves, Left Type ("Left Ventricular Hypertrophy") (III, 1)

The criteria for left hypertrophy are here entirely based on high R wave amplitudes in selected leads An overall relationship of these findings with left ventricular myocardial hypertrophy exists in clinical pathological studies but application of these criteria results in many individual misclassifications

G THE INTER-RELATIONS OF ELECTROCARDIOGRAPHIC FINDINGS AND PHYSICAL CHARACTERISTICS OF MIDDLE-AGED MEN

by Henry Blackburn, R W Parlin and Ancel Keys (Minneapolis)

The electrocardiogram (ECG) was employed in these studies because of its relevance to the identification of cardiac abnormalities and to prediction of risk of future disease (Blackburn *et al* 1960) The special problems in application of electrocardiography to population studies have been discussed elsewhere along with the efforts made to present in unambiguous terms the ECG findings of generally agreed interest (Blackburn *et al* 1960 Higgins *et al* 1963 Blackburn 1965)

In the appropriate parts of Section C above detailed distributions are given by area of all principal ECG abnormalities found on the initial examination in men aged 40 through 59 The method of sampling response rates and characteristics of these populations are reported in Section A and the standardized procedures for recording and classification of the ECG are noted in Section B ("Methods") above

The systematic tabulating is here made of the frequency of specified ECG abnormalities according to classes of major physical characteristics measured sum of subcutaneous skinfolds (Σ skinfolds) and relative body weight (RBW) systolic blood pressure (SBP) and diastolic blood pressure (DBP) and serum cholesterol (SC) The five ECG items selected are of interest in regard to their anatomic and functional correlates of myocardial infarction and hypertrophy and ischemia — large Q waves (Code I 1), left axis deviation of at least —30 degrees (Code II, 1), high amplitude R waves left type (Code III 1) negative T waves (Code V 1 2) and S-T segment depression immediately after a standard three-minute exercise test (Code XI 1—4)

In other reports relationships will be considered between these clearly defined ECG items and the prevalence of clinical manifestations of cardiovascular disease On follow-up study of the men the risk of subsequent heart disease and death associated with particular ECG findings will be ascertained If significant relationships are found it is necessary that the degree of association with other risk factors be estimated

In this analysis the values for each physical characteristic are arrayed within quinquennial age classes, providing a ranking by quintiles of each subject within his own age and area class Subjects having a given ECG abnormality are compiled according to where they fall along the quintile distribution of the physical characteristic The relation

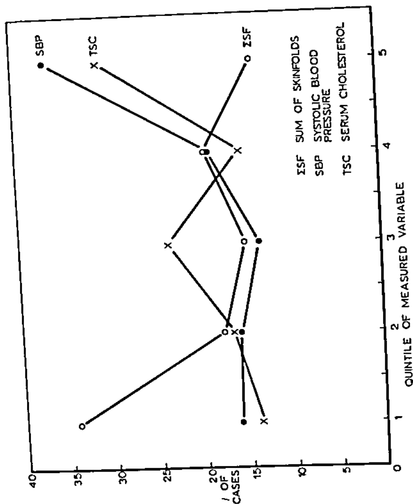

LARGE INFARCT Q WAVES (I 1) VERSUS
PHYSICAL CHARACTERISTICS
SBP
X TSC
ΣSF
ΣSF SUM OF SKINFOLDS
SBP SYSTOLIC BLOOD PRESSURE
TSC SERUM CHOLESTEROL
40
35
30
25
20
15
10
5
0
% OF CASES
1
2
3
4
5
QUINTILE OF MEASURED VARIABLE

Figure G1

TABLE G1

THE RELATIONSHIP OF LARGE Q WAVES (I 1) IN THE ELECTROCARDIOGRAM TO PHYSICAL CHARACTERISTICS OF MEN AGED 40 59 YEARS

AREA

ΣSF	USRR 2162	EF 815	WF 858	ZU 871	YS 669	YN 697	VK 510	MO 718	CR 980	IRR 766	CT 685	CU 529	TOTAL 10 260	PER CENT
Median <	15	4	4	6	0	1	2	2	5	3	0	2	44	
Cut >	11	3	2	3	0	2	3	2	0	1	1	1	29	
Quintile 1	8	3	1	2	0	1	1	1	4	3	0	1	25	34 2
2	6	1	2	2	0	0	1	1	0	0	0	0	13	17 8
3	3	1	2	2	0	0	1	0	1	0	0	1	11	15,1
4	6	1	1	0	0	1	2	2	0	0	0	1	14	19 2
5	3	1	0	3	0	1	0	0	0	1	1	0	10	13,7

All samples quintile 1 vs 5 Chi square = 5 65 (p < 025)

RBW	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median <	15	4	5	6	0	1	2	1	5	3	0	1	43	
Cut >	11	2	1	3	0	2	3	3	0	1	1	2	29	
Quintile 1	8	3	3	3	0	1	1	1	5	3	0	0	28	38 9
2	3	0	2	2	0	0	1	0	0	0	0	1	9	12,5
3	7	1	1	2	0	0	1	0	0	0	0	1	13	18 0
4	3	1	0	2	0	1	2	3	0	1	0	1	14	19,4
5	5	1	0	0	0	1	0	0	0	0	1	0	8	11 1

All samples quintile 1 vs 5 Chi-square = 10 12 (p < 005)

SBP	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median <	8	2	3	5	0	1	3	1	1	1	0	3	28	
Cut >	18	5	3	4	0	2	3	3	4	3	1	0	46	
Quintile 1	2	2	1	1	0	0	2	1	1	1	0	1	12	16,2
2	4	0	2	2	0	1	1	0	0	0	0	1	11	14,9
3	4	1	0	3	0	0	0	0	1	0	0	1	10	13 5
4	7	0	1	0	0	1	2	2	0	1	0	0	14	18 9
5	9	4	2	3	0	1	1	1	3	2	1	0	27	36 5

All samples quintile 1 vs 5 Chi square = 5 07 (p < 025)

DBP	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median <	9	2	3	5	0	1	5	1	3	2	0	2	33	
Cut >	17	5	3	4	0	2	0	3	2	2	1	1	40	
Quintile 1	1	1	0	1	0	0	2	1	1	0	0	1	8	11,0
2	5	0	2	3	0	0	3	0	2	1	0	0	16	21,9
3	6	1	2	2	0	2	0	0	0	1	0	2	16	21,9
4	7	2	0	0	0	0	0	2	1	1	0	0	13	17 8
5	7	3	2	3	0	1	0	1	1	1	1	0	20	27 4

All samples quintile 1 vs 5 Chi square = 4 35 (p < 05)

S CHOL	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median <	11	4	1	2	0	1	3	1	3	3	0	2	31	
Cut >	15	3	5	7	0	2	2	3	1	1	1	1	41	
Quintile 1	4	1	1	0	0	0	1	1	1	0	0	1	10	13,9
2	4	1	0	2	0	1	2	0	1	1	0	0	12	16,7
3	5	2	1	2	0	0	0	1	2	2	0	2	17	23,6
4	3	0	3	1	0	1	1	0	0	1	1	0	11	15 3
5	10	3	1	4	0	1	1	2	0	0	0	0	22	30 6

All samples quintile 1 vs 5 Chi square not significant

Total no men in each quintile = 2052
Total no men *above and below median = 5130*

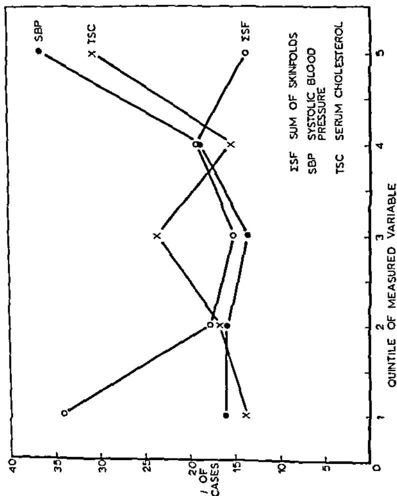

LARGE INFARCT Q WAVES (I,1) VERSUS
PHYSICAL CHARACTERISTICS
SBP
X TSC
ΣSF
ΣSF SUM OF SKINFOLDS
SBP SYSTOLIC BLOOD PRESSURE
TSC SERUM CHOLESTEROL
/ OF CASES
0
5
10
15
20
25
30
35
40
1
2
3
4
5
QUINTILE OF MEASURED VARIABLE

Figure G1

TABLE G1

THE RELATIONSHIP OF LARGE Q WAVES (I 1) *IN THE ELECTROCARDIOGRAM* TO PHYSICAL CHARACTERISTICS OF MEN AGED 40 59 YEARS

AREA

ΣSF	USRR 2162	EF 815	WF 858	ZU 871	YS 669	YN 697	VK 510	MO 718	CR 980	IRR 766	CT 685	CU 529	TOTAL 10 260	PER CENT
Median <	15	4	4	6	0	1	2	2	5	3	0	2	44	
Cut >	11	3	2	3	0	2	3	2	0	1	1	1	29	
Quintile 1	8	3	1	2	0	1	1	1	4	3	0	1	25	34 2
2	6	1	2	2	0	0	1	1	0	0	0	0	13	17 8
3	3	1	2	2	0	0	1	0	1	0	0	1	11	15.1
4	6	1	1	0	0	1	2	2	0	0	0	1	14	19.2
5	3	1	0	3	0	1	0	0	0	1	1	0	10	13.7

All samples quintile 1 vs 5 Chi square = 5 65 (p < 025)

RBW	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median <	15	4	5	6	0	1	2	1	5	3	0	1	43	
Cut >	11	2	1	3	0	2	3	3	0	1	1	2	29	
Quintile 1	8	3	3	3	0	1	1	1	5	3	0	0	28	38.9
2	3	0	2	2	0	0	1	0	0	0	0	1	9	12.5
3	7	1	1	2	0	0	1	0	0	0	0	1	13	18.0
4	3	1	0	2	0	1	2	3	0	1	0	1	14	19.4
5	5	1	0	0	0	1	0	0	0	0	1	0	8	11 1

All samples quintile 1 vs 5 Chi-square = 10 12 (p < 005)

SBP	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median <	8	2	3	5	0	1	3	1	1	1	0	3	28	
Cut >	18	5	3	4	0	2	3	3	4	3	1	0	46	
Quintile 1	2	2	1	1	0	0	2	1	1	1	0	1	12	16 2
2	4	0	2	2	0	1	1	0	0	0	0	1	11	14 9
3	4	1	0	3	0	0	0	0	1	0	0	1	10	13 5
4	7	0	1	0	0	1	2	2	0	1	0	0	14	18 9
5	9	4	2	3	0	1	1	1	3	2	1	0	27	36 5

All samples quintile 1 vs 5 Chi square = 5 07 (p < 025)

DBP	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median <	9	2	3	5	0	1	5	1	3	2	0	2	33	
Cut >	17	5	3	4	0	2	0	3	2	2	1	1	40	
Quintile 1	1	1	0	1	0	0	2	1	1	0	0	1	8	11.0
2	5	0	2	3	0	0	3	0	2	1	0	0	16	21.9
3	6	1	2	2	0	2	0	0	0	1	0	2	16	21.9
4	7	2	0	0	0	0	0	2	1	1	0	0	13	17 8
5	7	3	2	3	0	1	0	1	1	1	1	0	20	27 4

All samples quintile 1 vs 5 Chi square = 4 35 (p < 05)

S CHOL	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median <	11	4	1	2	0	1	3	1	3	3	0	2	31	
Cut >	15	3	5	7	0	2	2	3	1	1	1	1	41	
Quintile 1	4	1	1	0	0	0	1	1	1	0	0	1	10	13.9
2	4	1	0	2	0	1	2	0	1	1	0	0	12	16.7
3	5	2	1	2	0	0	0	1	2	2	0	2	17	23.6
4	3	0	3	1	0	1	1	0	0	1	1	0	11	15 3
5	10	3	1	4	0	1	1	2	0	0	0	0	22	30 6

All samples quintile 1 vs 5 Chi square not significant

Total no men in each quintile = 2052
Total no men above and below median = 5130

TABLE G2

THE RELATIONSHIP OF LEFT AXIS DEVIATION > 30 (II 1) IN THE ELECTROCARDIOGRAM TO PHYSICAL CHARACTERISTICS OF MEN AGED 40 59 YEARS

	AREA													
	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER
ΣSF	2162	819	858	871	669	697	510	718	980	766	685	529	10 260	CENT
Median <	40	11	21	14	9	19	10	23	21	15	19	5	207	
Cut >	24	13	18	21	14	21	7	21	20	15	13	5	192	
Quintile 1	20	5	8	4	5	14	1	7	9	6	8	3	90	22.6
2	22	5	10	8	4	5	7	10	10	6	11	1	88	22.1
3	14	4	4	7	1	4	3	10	9	7	2	2	67	16 8
4	17	5	7	11	5	8	1	10	5	6	4	3	72	18 1
5	12	5	10	15	8	9	4	7	8	5	7	1	81	20 4

All samples quintile 1 vs 5 Chi square not significant

RBW	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median <	30	17	18	19	7	19	7	16	18	16	13	3	183	
Cut >	34	7	1	16	16	21	10	9	21	14	17	7	212	
Quintile 1	18	6	5	5	4	9	2	5	8	3	6	1	72	18.
2	12	3	8	10	7	8	4	9	9	8	5	2	81	20.4
3	3	9	9	9	3	4	2	12	3	7	9	1	71	17.9
4	16	2		n	[illegible]	11	4	8	11	4	5	3	93	1.0
5	13	4	11	5	9	8	5	10	8	8	5	3	87	22 5

All samples quintile 1 vs 5 Chi square not sign f cant

SBP	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median <	33	12	19	18	7	19	4	21	23	9	23	6	194	
Cut >	31	12	(	17	15	21	13	23	18	21	9	4	04	
Quintile 1	12	4	4	4	2	8	1	4	10	5	10	2	81	20 4
2	16	6		4	3	7	3	8	7	[illegible]	8	4	5	18 8
3	9	3	4	8		9	3	9	8	4	5	1	65	16 3
4	9	6	10	4	8	8	4	7	9	8	5	2	80	20 1
5	18	5	9	10	7	8	6	11		1	4	1	97	24 4

All samples quintile 1 vs 5 Chi square not significant

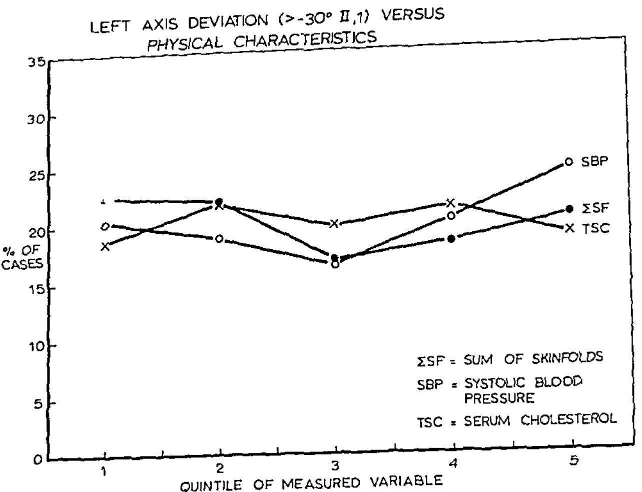
DBP	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median <	28	14	[illegible]	[illegible]	6	[illegible]	6	2	16	9	1	4	184	
Cut >	36	10	20	15	16	18	11	2	5	21	15	6	215	
Quintile 1	11	6	10	11	1	7	1	10	8	4	6	1	6	19 0
2	9	7	7	5	3	9	1	11	8	3	7	3	[illegible]	18 3
3	17	2	8	5	5	8	5	4	3	7	5	2	[illegible]	17.8
4	12	3	6	4	6	6	2	9	1	8	8		83	20 8
5	15	6	9	10	7	10	8	10	5	8	6	2	96	4 1

All s mples quintile 1 vs 5 Chi square not s gnificant

S CHOL	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median <	36	16	20	16	6	25	8	21	16	17	12	5	198	
Cut >	26	8	0	15	16	14	[illegible]	3	24	13	19	5	[illegible]	
Quintile 1	18	4	6	5	1	8		11	6	6	4	1	[illegible]	18 6
2	11	8	12	7	4	11	4	8	4	7	6	[illegible]	4	1 8
3	11	5	6	7	2	11	3	4	13	4	6	4	76	19.
4	12	3	8	5	7	5	6	11	11	4	9	1	9	1 2
5	10	4	8	7	8	4	2	10		5	6		2	18 6

All samples quintile 1 vs 5 Chi square not signif cant

Total no men in each qu ntile 2052
Total no men above and below median 5130



LEFT AXIS DEVIATION (>-30° II,1) VERSUS
PHYSICAL CHARACTERISTICS
% OF CASES
35
30
25
20
15
10
5
0
1
2
3
4
5
QUINTILE OF MEASURED VARIABLE
SBP
ΣSF
TSC
ΣSF = SUM OF SKINFOLDS
SBP = SYSTOLIC BLOOD PRESSURE
TSC = SERUM CHOLESTEROL

Figure G2

The inverse relationship of 'left hypertrophy' by ECG and body fatness and relative weight is shown in Table G3 and Figure G3 and is statistically significant in the analysis around the median cut-off value for skinfold obesity (chi-square median cut = 6 76, p < 01), and between upper and lower quintiles for RBW There is however an inverted U-shaped distribution which is unexplained A clear monotonic relation exists between high R amplitudes and increasing systolic blood pressure (chi-square quintile 1 vs 5 = 67 77 p < 0001) which is also present for diastolic pressure There is no consistent relation to serum cholesterol level throughout the areas but a slightly peaked distribution of the ECG item according to quintile class of serum cholesterol is found in the totals for all population samples and is unexplained

Negative T Waves (V, 1—2)

Negative T waves in specified ECG leads represent "non-specific" myocardial ischemia and other functional cellular phenomena as well as myocardial infarction and fibrosis In Table G4 and Figure G4 no evidence appears of an association of this finding with fatness overweight or serum cholesterol but a distinct increase in frequency of this finding occurs among the top 20 per cent of values for systolic and diastolic blood pressure The excess frequency is as striking among systolic hypertensives (chi-square quintile 1 vs 5 = 17 66 p < 0001) as it is among men in the upper 20 % of diastolic pressures

Post-exercise S-T Depression (XI, 1—4)

The ECG criteria employed here combine the presence of distinctly abnormal (0 1 mv or more) junctional S-T depression and the "ischemic"-type horizontal or sagging S-T segment depression These are subjects with no abnormal S-T depression in their resting ECGs and would be considered clinically to have isolated "positive" or "borderline" ECG exercise responses In Table G5 and Figure G5 the occurrence of these ECG exercise responses clearly relates to increasing fatness (chi-square quintile 1 vs 5 = 23 40 p < 001), increasing relative weight (chi-square quintile 1 vs 5 = 7 09, p < 01) and blood pressure (chi-square quintile 1 vs 5 SBP = 39 75 p < 0001) but the relation to serum cholesterol level is not statistically significant

Discussion

The relationship of specified ECG abnormalities to physical characteristics in these pooled samples of middle-aged men raises many questions the first concerns their overall validity This depends in turn, on the reliability of the individual measures and ECG classifications as well as the appropriateness of lumping data from such varied cultures Finally, among the numerous comparisons made there is the possibility of chance findings of statistically significant differences

Infarct Q Waves (I 1) Reading agreement in this Laboratory is on the order of 90 per cent within and between observers on the presence or absence of item I 1 Q waves in the ECG and the clinical relevance of this finding to myocardial infarct is well established and widely accepted (Blackburn *et al* 1960) Though the numbers of large Q waves in these total populations are small (0 7 % of all men aged 40—59) the concentration of 'old infarct" cases within classes of the physical characteristics is fairly consistent throughout the samples and is in the same direction for

TABLE G3

THE RELATIONSHIP OF
HIGH AMPLITUDE R WAVES (I EFT TYPE) (III, 1)
IN THE ELECTROCARDIOGRAM TO PHYSICAL CHARACTERISTICS
OF MEN AGED 40 59 YEARS

AREA

ΣSF	USRR 2162	EF 815	WF 858	ZU 871	YS 669	YN 697	VK 510	MO 718	CR 980	IRR 766	CT 685	CU 529	TOTAL 10 260	PER CENT
Median	27	77	83	22	9	41	24	17	32	18	19	22	391	
Cut	6	68	56	15	10	38	38	7	23	18	16	18	323	
Quintile 1	7	24	22	5	3	16	7	7	10	7	5	9	122	17 1
2	13	36	41	12	3	19	12	6	15	8	8	7	180	25 2
3	14	37	33	8	4	15	15	4	11	3	11	11	166	23 2
4	9	27	29	7	5	17	16	5	11	5	5	10	146	20 4
5	10	21	14	5	4	12	12	2	8	3	6	3	100	14 0

All samples quirtile 1 vs 5 Chi square not significant

RBW

RBW	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median	23	68	76	17	8	48	25	16	33	20	22	20	376	
Cut	29	70	63	20	11	31	37	8	22	6	13	0	336	
Quintile 1	8	29	28	10	4	17	10	9	13	5	5	8	146	20.
2	15	22	31	5	2	19	10	4	18	14	11	9	160	22 5
3	10	40	32	6	4	18	14	5	9	3	8	9	158	22.2
4	4	31	29	6	5	14	15	4	9	4	6	9	136	19.0
5	15	22	19	10	4	11	13	2	6	0	5	5	112	15 7

All samples quintile 1 vs 5 Chi square – 4 50 (p < 05)

SBP

SBP	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median	14	59	55	17	8	31	17	8	18	5	11	12	255	
Cut	39	8	84	20	11	48	45	16	36	21	24	28	458	
Quintile 1	4	21	21	10	1	10	5	2	6	0	2	6	88	12.3
2	4	25	17	3	6	14	7	2	8	4	8	3	101	14.2
3	8	22	32		3	16	16	5	10	6	5	9	137	19.2
4	12	34	35	6	5	15	15	5	11	5	7	7	157	22 0
5	25	43	34	13	4	24	19	10	19	11	13	15	230	32 2

All ampl s quintile 1 s 5 Chi squa e = 67 77 (p < 0001)

DBP

DBP	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median	16	68	74	13	8	0	22	10	16	11	11	17	296	
Cut	37	77	6	29	11	49	40	14	38	15	24	23	417	
Quintile 1	4	3	37	7	3	11	6	5	5	2	6	7	116	16 3
2	8	30	21	5	2	13	10	3	9	4	3	6	114	16 0
3	9	27	27	4	6	17	14	3	6	10	5	9	137	19 2
4	8	33	22	10	5	16	12	7	17	2	12	5	149	20.9
5	24	32	32	11	3	22	20	6	17	8	9	13	197	27.6

All amples quintile 1 vs 5 Chi squa e 22 14 (p < 0001)

S CHOL

S CHOL	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median	31	80	76	18	5	41	26	13	24	17	13	22	346	
Cut	21	[illegible]	[illegible]	17	14	36	36	11	30	9	[illegible]	16	339	
Quintile 1	12	28	27	5	0	17	12	5	10	8	7	9	135	19.1
2	10	31	33	8	2	19	10	5	9	6	9	10	152	21 6
3	16	34	29	9	5	11	19	4	13	4	6	8	160	22.7
4	9	28	22	8	10	17	10	6	15	6	9	4	144	20.4
5	5	24	27	5	2	13	11	4	7	2	7	7	114	16.2

All sample q intile 1 vs 5 Chi square not gn f ant

T ta no m in ea h quint l 2052
Total no m n abo e nd b low med an 5130

The inverse relationship of 'left hypertrophy' by ECG and body fatness and relative weight is shown in Table G3 and Figure G3 and is statistically significant in the analysis around the median cut-off value for skinfold obesity (chi-square, median cut = 6 76, $p < 01$) and between upper and lower quintiles for RBW There is however an inverted U-shaped distribution which is unexplained A clear monotonic relation exists between high R amplitudes and increasing systolic blood pressure (chi-square, quintile 1 vs 5 = 67 77, $p < 0001$), which is also present for diastolic pressure There is no consistent relation to serum cholesterol level throughout the areas, but a slightly peaked distribution of the ECG item according to quintile class of serum cholesterol is found in the totals for all population samples and is unexplained

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Discussion

The relationship of specified ECG abnormalities to physical characteristics in these pooled samples of middle-aged men raises many questions the first concerns their overall validity This depends in turn, on the reliability of the individual measures and ECG classifications as well as the appropriateness of lumping data from such varied cultures Finally among the numerous comparisons made there is the possibility of chance findings of statistically significant differences

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TABLE G4

THE RELATIONSHIP OF
NEGATIVE T WAVES (V 1 & 2)
IN THE ELECTROCARDIOGRAM TO PHYSICAL CHARACTERISTICS
OF MEN AGED 40 59 YEARS

ESF		USRR 2162	EF 815	WF 858	ZU 871	YS 669	YN 697	VK 510	MO 718	CR 980	IRR 766	CT 685	CU 529	TOTAL 10 260	PER CENT
Median	<	19	12	6	7	2	4	3	4	11	2	1	4	75	
Cut	>	11	15	7	9	1	8	1	4	6	3	3	7	75	
Quintile	1	6	5	4	3	0	0	1	2	6	6	0	1	28	20.0
	2	11	6	0	2	1		2	1	3	1	1	-	32	2[illegible].8
	3	2	3	3	4	1	3	1	1	3	1	0	1	23	16.4
	4	5	5	2	3	1	1	0	2	2		2	4	29	20.7
	5	6	8	4	4	0	6	0	2	3	1	1	3	28	20.0

All samples quintile 1 vs 5 Chi square not significant

RBW		USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median	<	16	12	5	8	2	2	1	4	10	2		3	67	
Cut	>	12	14	8	8	1	10	3	4	7	3	2	8	80	
Quintile	1	7	5	3	4	0	0	0	2	7	0	0	2	30	20.4
	2	6	5	1	1	2		0	0	3	0		1	23	15.6
	3	4	5	2	3	0	1	1	2	1	3	1	0	23	15.6
	4	6	4	3	2	1	3	3	2	4	0	0	3	31	21.1
	5	5	7	4	6	0	6	0	2	2	2	1	5	40	27 2

All samples quintile 1 vs 5 Chi square not significant

SBP		USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median	<	7	10	5	8	2	0	1	3	7	1	2	2	48	
Cut	>	23	17	8	8	1	12	3	5	10	4	2	9	102	
Quintil	1	3	5	4	1	1	0	1	2	5	1	0	1	24	16.0
	2	4	4	1	4	1	0	0	0	2	0	1	1	18	12.0
	3	4	1	0	4	0	1	0	3	1	1	2	1	18	12.0
	4	7	3	2	2	1	5	1	1	0	0	0	4	26	17 3
	5	12	14	6	5	0	6	2	2	9	3	1	4	64	42 7

All samples quintile 1 vs 5 Chi square = 17 66 (p < 0001)

DBP		USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median	<	12	8	8	6	2	3	0	4	7	0	3	4	57	
Cut	>	18	19	5	10	1	9	4	4	10	5	1	7	93	
Quintile	1	3	4	5	0	1	0	0	2	3	0	0	1	19	12.7
	2	4	2	2	5	1	1	0	1	3	0	2	2	23	15.3
	3	7	3	3	2	0	2	1	1	2	1	1	1	24	16.0
	4	5	7	1	2	0	3	0	1		1	0	4	29	19 3
	5	11	11	2	7	1	6	3	3	4	3	1	3	55	36.7

All samples quintile 1 vs 5 Chi square = 16 86 (p < 0001)

S CHOL		USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Median	<	4	13	14	4	6	2	4	5	3	7	8	2	73	
Cut	>	0	15	13	1	7	1	0	7	5	9	7	2	73	
Quintil	1	2	1	2	4	2	1	-	2	0	1	3	0	21	14.4
	2	2	9	8	0	4	1	2	3	3	5	4	1	42	28 8
	3	0	8	6	0	2	1	0	2	2	5	3	2	32	21 9
	4	0	4	6	1	1	0	0	1	1	3	2	0	23	15 8
	5	0	6	5	0	4	0	0	4	2	2	3	1	28	19.2

All samples quintile 1 vs 5 Chi square not significant

Total no men in each quintile = 2052
Total no men above and below median 5130

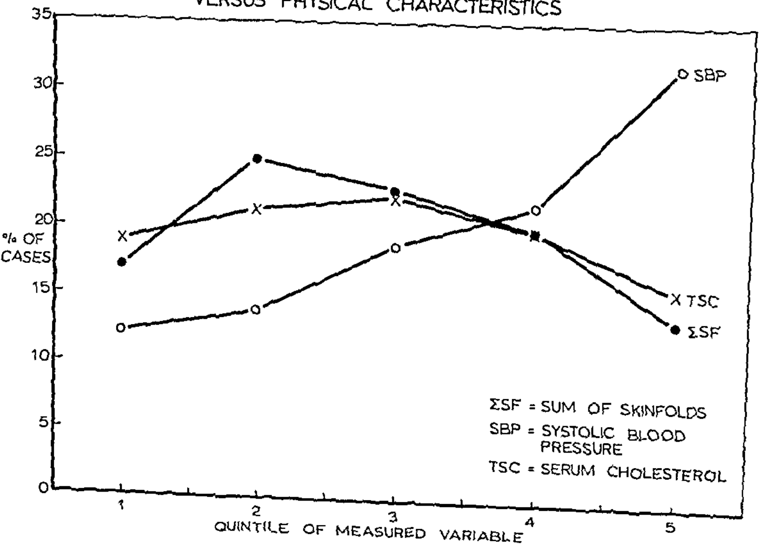

HIGH AMPLITUDE R WAVES (LEFT-TYPE III,1)
VERSUS PHYSICAL CHARACTERISTICS
% OF CASES
35
30
25
20
15
10
5
0
1
2
3
4
5
QUINTILE OF MEASURED VARIABLE
SBP
TSC
ΣSF
ΣSF = SUM OF SKINFOLDS
SBP = SYSTOLIC BLOOD PRESSURE
TSC = SERUM CHOLESTEROL

Figure G3

TABLE G5

THE RELATIONSHIP OF
POST EXERCISE S T DEPRESSIO N (XI, 1 4)
IN THE ELECTROCARDIOGRAM TO PHYSICAL CHARACTERISTICS
OF MEN AGED 40 59 YEARS

	AREA													
	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
ΣSF	2162	815	858	871	669	697	510	718	980	766	685	529	10 260	
Median	71	10	10	14	4	10	10	16	21	24	17	11	218	
Cut	8	14	18	25	7	15	6	25	22	39	24	22	301	
Qu ntil 1	30	5	7	6	1	5	3	3	9	9	4	4	81	15.6
2	31	4	6	2	1	3	5	10	6	10	9	3	90	17 3
3	25	4	4	8	3	3	3	5	9	11	9	9	93	17 9
4	34	6	5	12	0	5	1	7	7	13	5	6	101	19 5
5	36	5	11	11	6	9	4	16	12	19	14	11	154	29 7

All samples quintile 1 vs 5 Chi square = 23 40 (p < 0001)

RBW

	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Med an	71	13	11	15	3	8	9	16	20	26	16	11	219	
Cut	82	11	16	24	8	17	7	25	23	36	25	22	296	
Quintile 1	30	6	4	5	1	5	5	4	9	9	6	4	88	17.1
2	27	3	6	6	2	2	4	11	4	7	7	5	84	16.3
3	28	7	4	9	0	5	1	4	13	15	7	6	99	19.2
4	31	4	5	12	2	4	2	11	12	14	10	10	117	22.7
5	37	4	8	7	6	9	4	11	5	17	11	8	127	24 7

All ampl s quintile 1 vs 5 Chi square – 7 09 (p < 01)

SBP

	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
M d an	62	6	8	12	7	8	7	17	15	21	16	12	191	
Cut	94	17	20	27	4	17	9	24	28	41	25	21	327	
Qu ntile 1	15	2	3	7	2	2	1	7	3	7	7	4	60	14.6
2	27	3	5	2	3	2	3	6	8	7	8	6	80	15.4
3	35	3	3	7	2	8	4	8	9	12	4	7	101	19.[illegible]
4	41	7	8	6	1	6	1	10	14	21	6	6	127	24.5
5	38	8	9	17	3	7	7	10	10	15	16	10	150	29 0

All sampl s quintile 1 vs 5 Chi square 39 75 (p < 0001)

DBP

	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
Med an	65	7	10	20	6	8	9	19	14	22	18	13	211	
C t	91	16	18	19	5	17	7	22	29	40	23	22	[illegible]09	
Quintile 1	28	3	5	7	5	3	[illegible]	7	6	5	8	5	84	16.2
2	29	3	3	10	1	2	3	7	4	11	6	6	[illegible]5	16.4
3	25	5	3	6	1	9	5	11	11	14	7	6	103	19.9
4	38	6	10	8	2	3	2	4	10	18	6	6	113	21 8
5	36	6		8	2	8	4	12	12	14	14	10	133	25 7

All samples quintile 1 vs 5 Chi square = 11 21 (p < 001)

S CHOL

	USRR	EF	WF	ZU	YS	YN	VK	MO	CR	IRR	CT	CU	TOTAL	PER CENT
M d n	79	17	13	15	5	12	8	19	14	31	15	15	241	
C t	[illegible]4	7	15	23	8	12	[illegible]	22	2[illegible]	31	24	17	2[illegible]0	
Q int l 1	31	4	5	3	1	5	4	6	8	12	[illegible]	9	[illegible]0	17 6
2	32	9	4	6	2	4	1	10	5	15	10	3	101	19 8
3	31	8	4	10	1	3	6	4	9	12	6	8	10[illegible]	20.0
4	24	1	5	12	4	7	2	12	10	11	8	6	102	20.0
5	35	2	10	7	3	5	3	9	11	12	13	6	116	22.7

All amples quintile 1 5 Chi square not gnificant

T t no m n in h q ntile 2052
T t l no m n abo and below median 5130

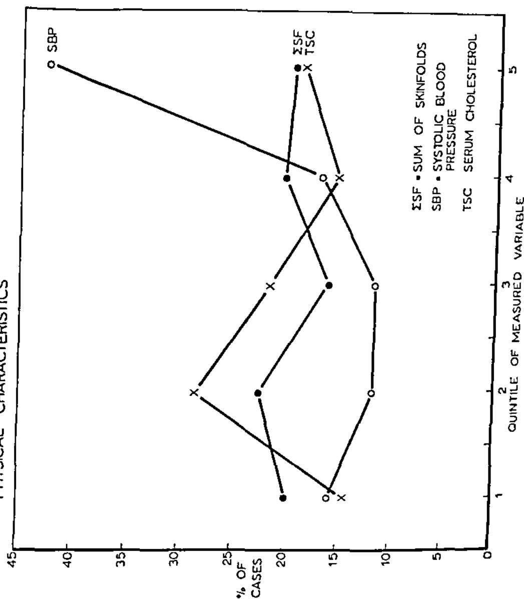

NEGATIVE T WAVES (V,1-2) VERSUS
PHYSICAL CHARACTERISTICS
SBP
ΣSF
TSC
ΣSF • SUM OF SKINFOLDS
SBP • SYSTOLIC BLOOD PRESSURE
TSC SERUM CHOLESTEROL
% OF CASES
45
40
35
30
25
20
15
10
5
0
1
2
3
4
5
QUINTILE OF MEASURED VARIABLE

Figure G4

each pair of the highly inter-correlated variables of weight-obesity and systo-lic-diastolic pressure (Table G1)

The distinct association of old infarct so described with the thinner-lighter men and the absence of a stronger association with serum cholesterol are somewhat unexpected The Q waves are a hard core of cases with manifest coronary heart disease, representing but a fraction of all those with anatomic or functional myocardial damage and coronary artery disease, and the relationships found are after the event The proportion of these ECG cases which were clinically silent" is being investigated The effects of the disease itself and in some cases the therapeutic adjustments made after the attack" may explain in part the cross-sectional relationships found Conclusions about future disease risk based on information from cross-sectional analyses may of course be biased and the relative strength of risk factors calculated from prevalence and incidence studies is a subject of general interest and study in cardiovascular epidemiology These findings on the Q wave confirm however follow-up information available that elevated arterial blood pressure and serum cholesterol are more important risk factors for myocardial infarction than are overweight or obesity (Keys *et al* 1963 Kannel *et al* 1964)

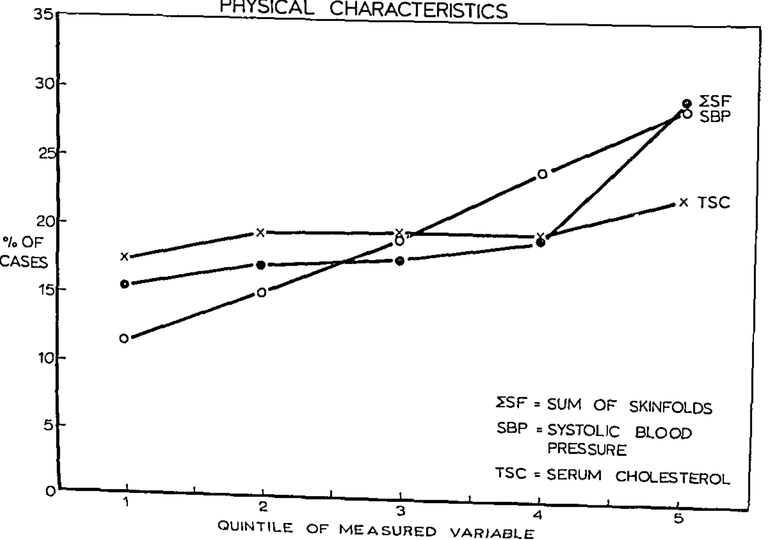
Left Axis Deviation $\geq -30°$ (II 1) This ECG criterion is read with considerable reliability The leftward and upward orientation of the frontal plane QRS vector can be caused either by anatomical left ventricular hypertrophy or by alteration of the time course of depolarization by myocardial infarction and fibrosis Both prevalence and incidence data concerning the clinical importance of this phenomenon indicate an important association with heart disease (Harlan *et al* 1962)

Here marked "abnormal" left axis occurring in 4 per cent of all men ages 40—59 has no significant relationship among the total of middle-aged men to their characteristics of body build blood pressure or blood cholesterol The ECG findings of left axis deviation may thus provide information independent of the other risk factors in assessing risk of future disease Follow-up data from these studies on the predictive import of left axis will be of interest

"Left Ventricular Hypertrophy (III 1) The different frequencies of occurrence of high amplitude R waves in the samples is striking from less than 3 per cent in U S railmen to 12 per cent in Slavonia (YN) and 17 per cent in Finland Systematic area differences due to different ECG apparatus or technique are unlikely since standard methods were employed and amplitude calibration was applied to all records The criteria used involve high QRS amplitudes in any of several ECG leads which from other studies might be expected to be roughly 70 per cent sensitive in detection of anatomic hypertrophy and about 70 per cent specific for identification of those truly without cardiac hypertrophy

Questions about the effect on surface potential differences of different heart sizes relative to chest size and body weight and about the effect of proximity of the heart to the chest wall are among the more complex in electrophysiology It is however common clinical experience to find largest ventricular complexes in the ECGs of men with very thin chests in children and in highly trained athletes

The distribution of ECG "left hypertrophy according to body build is inconsistent between areas and this plus the U-shaped frequency distribution of the item renders attempts at interpretation hazardous Clearly however increments in the cardiac load from arter-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PHYSICAL CHARACTERISTICS
35
30
25
20
15
10
5
0
% OF
CASES
ΣSF
SBP
TSC
ΣSF = SUM OF SKINFOLDS
SBP = SYSTOLIC BLOOD PRESSURE
TSC = SERUM CHOLESTEROL
1
2
3
4
5
QUINTILE OF MEASURED VARIABLE

Figure G5

However the S-T response which is another ECG item clinically related to myocardial ischemia though more elusive and transient than T waves or infarction shows here no relationship to an isolated individual measure of serum cholesterol Deaths from clinical attacks of myocardial infarction are highly related to and the risk crudely predicted by the serum cholesterol level in clinical health as well as by post-exercise ECG responses of the S-T There is no *a priori* necessity that serum cholesterol level and the S-T response be highly correlated and here it is clear that they are not

The relationships found overall are similar to those found within the U S railway study above (Blackburn *et al* 1961) and to those found in the resting ECG of men over age 40 in the Tecumseh community study of the University of Michigan (Ostrander *et al* 1965)

Summary

The inter-relationships between measured physical characteristics and several objectively categorized electrocardiographic abnormalities are examined among men aged 40—59 in large total *population* samples Despite many limitations this may be the only way in which an approximation of the true inter relationships may be obtained Large Q waves equivalent to an anatomic diagnosis of myocardial infarction and most gross ECG abnormalities occur too rarely to be studied in detail within one population and pooling of men of similar age from many areas is made here *as a practical* approach to a preliminary look at the relationships

More or less expected associations were found *in* some cases readily explainable under existing hypotheses and facts For example, infarct Q waves high left hypertrophy type R waves negative T waves and "positive" (depressed) S-T responses after effort tests are moderately to highly associated with increments in arterial blood pressure and left 'hypertrophy' is unrelated to serum cholesterol Less expected however is *the definite relationship* found between infarct Q waves and being lightweight and thin and the impressive absence of *any significant* relationship between other "coronary" ECG patterns (i e negative T waves and positive exercise tests) and serum cholesterol Marked left axis deviation ominously regarded clinically is unrelated to any of the other measured risk factors Finally all positive associations of ECG abnormalities with arterial blood pressure are more distinct with the systolic than with the diastolic blood pressure levels

The implications are clear for evaluation of the predictive import of these ECG items in follow-up studies among middle-aged men In particular study of the post-exercise responce of the S-T segment as a risk factor for subsequent disease must be made with consideration of the association with extreme obesity and especially with blood pressure Nothing is yet known about the predictive import of the exercise ECG response in the absence of these conditional factors

INTER RELATIONS OF ELECTRO CARDIOGRAPHIC FINDINGS AND CIGARETTE SMOKING HABIT

There is evidence that cigarette smoking habit is significantly associated with risk of future coronary disease from follow-up study of volunteer groups (Doll and Hill 1956 Hammond and Horn 1958 Doyle *et al* 1962) The *inter-relations* of smoking with diagnostic and predictive ECG items is therefore of interest

Detailed smoking habit and ECG

ial blood pressure are reflected in an excess of high voltages in the body surface ECG

Negative T Waves (V, 1—2) Negative T waves of the type defined are non-specific indicators of myocardial damage or ischemia They are read with high repeatability, and occur about twice as frequently among these middle-aged men as do clear ECG signs of old myocardial infarction

In working population groups the usual clinical considerations among hospital and patient groups about the probable genesis of negative T waves do not hold (e g, acute pericarditis or myocarditis drug and electrolyte effects etc) because of the great rarity of transient influences on the T wave at any given time in such populations The records are taken in a random time relationship to prior meals and the procedure is the same in all of the areas Meal or glucose effects on the T wave which may exist (Ostrander and Weinstein, 1964) cannot account for the strong relationship to elevated blood pressure

Finally the occurrence of cases with manifest valvular heart disease is extremely rare in total adult populations and parasitic heart involvement does not occur in these areas It is therefore probable that we are dealing with a crude statistic related to myocardial ischemia or damage from coronary artery disease These findings are more likely to exist silently in a population than are infarctions (manifested by large Q waves) so that their interrelations could be conceivably of more interest than other ECG abnormalities considered tantamount to frank clinical disease

Despite the greater numbers of T than Q wave cases observed among all areas no significant relationship of negative T waves to obesity is found The concentration of negative T waves in the *highest* quintile of blood pressure *is entirely* responsible for the association observed with blood pressure. Elevated blood pressure appears to be the most important factor in the overall occurrence of negative T waves in a population while the factors responsible for negative T waves are unrelated to serum cholesterol

Post-exercise S-T Depression (XI 1—4) The ECG exercise test is difficult to apply and interpret in population studies but is of great general interest (Report of Research Committee ISC 1964) Coding of lesser degrees of S-T depression is unreliable for the individual case which is an important consideration in studying such interrelationships Observer agreement is high only for item XI, 1, the more marked S-T depression category The original published code (Blackburn et al 1960) does not adequately distinguish junctional from ischemic-type depression and until more is known about their relative significance they should be separately analyzed especially in a study of detailed inter-relationships Considerable opportunity exists therefore for the finding of inexplicable and perhaps meaningless relationships

On the other hand S-T depression in the post-exercise ECG provides the largest numbers of individual ECG phenomena for analysis The interrelations found with the exercise ECG test are moreover either quite strong or very weak without areas of borderline significance It appears safe from Table G 5 and Figure G 5 to assume some overall relation of positive exercise ECG response (? myocardial ischemia) to extreme obesity and a very strong relationship between the ECG and an exercise load superimposed on increasing levels of arterial pressure These are reasonable and not unexpected results interpretable by accepted principles

However the S-T response which is another ECG item clinically related to myocardial ischemia though more elusive and transient than T waves or infarction shows here no relationship to an isolated individual measure of serum cholesterol Deaths from clinical attacks of myocardial infarction are highly related to and the risk crudely predicted by the serum cholesterol level in clinical "health as well as by post exercise ECG responses of the S-T There is no a priori necessity that serum cholesterol level and the S-T response be highly correlated and here it is clear that they are not

The relationships found overall are similar to those found within the U S railway study above (Blackburn *et al* 1961) and to those found in the resting ECG of men over age 40 in the Tecumseh community study of the University of Michigan (Ostrander *et al* 1965)

Summary

The inter relationships between measured physical characteristics and several objectively categorized electrocardiographic abnormalities are examined among men aged 40—59 in large total population samples Despite many limitations this may be the only way in which an approximation of the true inter relationships may be obtained Large Q waves equivalent to an anatomic diagnosis of myocardial infarction and most gross ECG abnormalities occur too rarely to be studied in detail within one population and pooling of men of similar age from many areas is made here as a practical approach to a preliminary look at the relationships

More or less expected associations were found in some cases readily explainable under existing hypotheses and facts For example, "infarct Q waves" high left hypertrophy" type R waves negative T waves and positive (depressed) S-T responses after effort tests are moderately to highly associated with increments in arterial blood pressure and left hypertrophy is unrelated to serum cholesterol Less expected however is the definite relationship found between infarct Q waves and being lightweight and thin and the impressive absence of any significant relationship between other coronary" ECG patterns (i e negative T waves and positive exercise tests) and serum cholesterol Marked left axis deviation ominously regarded clinically is unrelated to any of the other measured risk factors Finally all positive associations of ECG abnormalities with arterial blood pressure are more distinct with the systolic than with the diastolic blood pressure levels

The implications are clear for evaluation of the predictive import of these ECG items in follow-up studies among middle aged men In particular study of the post-exercise responce of the S-T segment as a risk factor for subsequent disease must be made with consideration of the association with extreme obesity and especially with blood pressure Nothing is yet known about the predictive import of the exercise ECG response in the absence of these conditional factors

INTER-RELATIONS OF ELECTRO CARDIOGRAPHIC FINDINGS AND *CIGARETTE SMOKING HABIT*

There is evidence that cigarette smoking habit is significantly associated with risk of future coronary disease from follow-up study of volunteer groups (Doll and Hill 1956 Hammond and Horn 1958 Doyle *et al* 1962) The inter-relations of smoking with diagnostic and predictive ECG items is therefore of interest

Detailed smoking habit and ECG

classification codes are contained in the Appendix In brief, the smoking classification employed for this analysis is as follows

Never — this group consists predominantly of those who never regularly smoked cigarettes, but because of the necessity to simplify the classification and because of the paucity among these groups, of exclusively pipe or cigar smokers the latter are contained in this category

Occasional and Light — less than 1 cigarette daily was classified only for the U S Railroad men, and the light class consists of regular smokers of 1 through 9 cigarettes daily

Moderate — *regular smokers of 10* through 19 cigarettes daily

Heavy — regular smokers of 20 or more cigarettes daily

Stopped — the stopped smokers class is based on the current history given on examination without regard to duration since stopping duration or amount of prior smoking reason for stopping or current history with regard to cigar or pipe smoking

Since both electrocardiographic findings and smoking habit are age-related between 40 to 60 years detailed analysis was made for each ECG item according to age quinquennium and smoking class These findings will be discussed though the tabular and graphic relationships for simplicity are based on *age-adjusted values The age-specific* rate per 1 000 men was calculated for each of the four age classes summed and divided by four The material for all areas is pooled

Large Q Waves (I 1) *A trend by* age in large "infarct" Q waves occurs but as seen in Table G6 and Figure G6 there is no clear association between the prevalence of this item and smoking habit *Stopped smokers* have the highest age-adjusted rate of "infarct" Q waves (10 7 per 1 000) and persons who have never smoked the lowest (2 1 per 1 000) Moderate and heavy smokers though lying between *these extremes have rates that are* comparable to those for the stopped smokers

Left Axis Deviation ≥ —30° (II, 1) No significant association between the existence of marked left axis deviation and smoking habit is found in the age-adjusted rates in Table G7 and Figure G6 Though the stopped smokers have a noticeably lower prevalence of this finding, prevalences in the other three smoking categories are indistinguishable

High Amplitude R Waves Left Type (III, 1) *In Table G8 and Figure G6* it is seen that stopped smokers have the highest rates of 'left hypertrophy" and that heavy smokers have substantially lower rates than other men The difference between prevalence rates for heavy smokers (60 1 per 1 000) and all other men (86 4 per 1 000) is statistically significant ($d = 26.3$ S E $= 6\ 65$ $p = 0001$)

Negative T Waves (V 1—2) An age trend exists for negative T waves in the resting ECG In Table G9 and Figure G6 there is a decreasing rate for this item according to intensity of smoking, *heavy smokers having the* lowest rate (8 1 per 1 000) Again the stopped smokers show an interesting departure from the other groups negative T *waves being 3 times as frequent* among them as among heavy smokers

Post-exercise S-T Depression (XI, 1—4) A consistent increase by age occurs in combined junctional and *segmental S-T depressions in the ECG* taken after standard exercise In Table G10 and Figure G6 there is a trend downward in prevalence of this finding according to increased smoking intensity *Again the highest rate occurs* among the heterogeneous group of stopped smokers

TABLE G6

Frequency (f) of large Q waves (Code I 1) in the electrocardiograms of men age 40 59 years by smoking habit class Rate is age adjusted rate per 1000 men

AREA	Stopped Smoking		Never Smoked		Light & Moderate Regular Smokers		Heavy Smokers	
	f	rate	f	rate	f	rate	f	rate
U S Railroad Men	4	9 3	3	7 2	11	15 2	9	19 3
East Finland	4	29 5	0	0 0	2	6 4	1	3 6
West Finland	1	6 0	0	0 0	2	7 7	3	22 0
Zutphen	5	56 6	0	0 0	4	7 8	0	0 0
Dalmatia	0	0 0	0	0 0	0	0 0	0	0 0
Slavonia	0	0 0	0	0 0	3	9 7	0	0 0
Velika Krsna	0	0 0	2	7 4	2	9 4	1	14 7
Montegiorgio	1	7 0	0	0 0	2	6 4	1	11 9
Crevalcore	0	0 0	0	0 0	4	8 4	1	5 6
Rome Railroad Men	1	6 4	1	10 4	1	6 1	1	3 5
Crete	0	0 0	0	0 0	0	0 0	0	0 0
Corfu	1	13 9	0	0 0	2	8 6	0	0 0
All areas combined	17	10 7*	6	2 1*	33	7 1*	17	6 7*

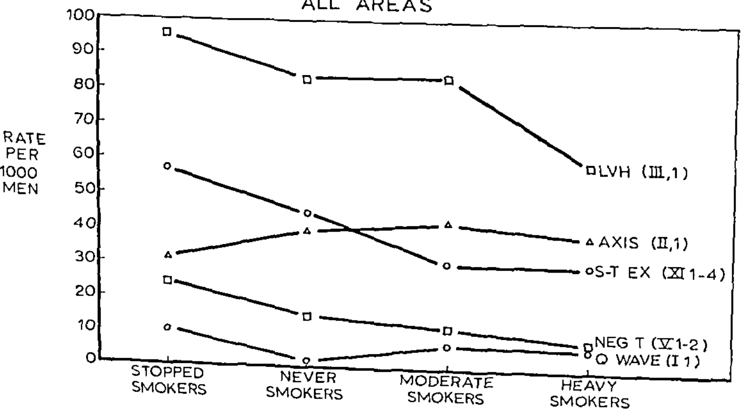
* Average of the rates for all areas

TABLE G7

Frequency (f) of left axis deviation > 30° (Code II 1) in the electrocardiograms of men age 40 59 years by smoking habit class Rate is age adjusted rate per 1000 men

AREA	Stopped Smoking		Never Smoked		Light & Moderate Regular Smokers		Heavy Smokers	
	f	rate	f	rate	f	rate	f	rate
U S Railroad Men	10	22 9	17	37 2	27	39 5	11	22 5
East Finland	1	6 8	4	33 2	11	38 0	8	34 4
West Finland	7	47 9	9	40 6	14	40 4	10	75 8
Zutphen	4	47 0	9	62 6	21	37 0	1	8 3
Dalmatia	1	10 9	5	23 5	11	48 2	6	33 3
Slavonia	2	18 3	8	43 9	20	62 4	10	75 2
Velika Krsna	2	33 3	9	38 6	7	41 5	1	15 6
Montegiorgio	8	72 6	12	65 2	18	51 0	5	77 5
Crevalcore	4	30 7	12	49 2	19	43 4	5	29 9
Rome Railroad Men	8	57 6	5	30 8	13	44 5	7	31 4
Crete	3	22 8	8	50 6	9	49 6	12	54 1
Corfu	1	13 9	1	8 6	6	25 6	2	15 1
All areas combined	51	32 0*	99	40 3*	176	43 4*	78	39 4*

* Average of the rates for all areas



RELATIONSHIP OF ELECTROCARDIOGRAPHIC FINDINGS TO
CIGARETTE SMOKING HABIT IN
MEN 40-59
ALL AREAS
RATE PER 1000 MEN
100
90
80
70
60
50
40
30
20
10
0
STOPPED SMOKERS
NEVER SMOKERS
MODERATE SMOKERS
HEAVY SMOKERS
LVH (III,1)
AXIS (II,1)
S-T EX (XI 1-4)
NEG T (V 1-2)
Q WAVE (I 1)

Figure G6

TABLF G8

Frequency (f) of high amplitude R waves left type (Code III 1) in the electrocardiograms of men age 40 59 years by smoking habit class Rate is age adjusted rate per 1000 men

AREA	SMOKING HABIT CLASS Stopped Smoking		Never Smoked		Light & Moderate Regular Smokers		Heavy Smokers	
	f	rate	f	rate	f	rate	f	rate
U S Railroad Men	16	35 6	16	35 5	16	21 8	6	11 7
East Fi land	30	210 0	22	184 9	59	193 6	35	135 4
West Finland	23	148 8	33	155 0	63	173 3	18	140 8
Zutphen	[illegible]	23 5	5	64 3	29	52 4	2	17 2
Dalmatia	2	19 2	8	39 [illegible]	8	36 4	1	6 1
Slavonia	14	158 8	19	114 9	34	117 3	11	77 1
Velika Krana	8	146 2	32	156 2	12	163 7	10	145 8
Monteg orgio	5	57 6	2	9 1	15	43 8	[illegible]	22 8
Crevalcore	13	109 5	12	47 0	24	58 6	6	36 2
Rom Railroad Men	6	50 8	5	38 3	11	43 3	4	14 5
Crete	7	55 6	8	50 6	12	66 6	8	39 2
Co fu	9	134 1	14	111 5	9	41 0	8	74 4
A l a eas combined	135	95 8*	176	83 9*	292	84 3*	111	60 1*

* Ave age of the rates for all areas

TABLE G9

Freq ncy (f) of negati e T waves (Code V 1 2) in the electrocardiograms of men age 40 59 y ar by smoking habit class Rate is age adjusted rate per 1000 men

AREA	*SMOKING HABIT CLASS* Stopped Smoking		Never Smoked		Light & Moderate Regular Smokers		Heavy Smokers	
	f	rate	f	rate	f	rate	f	rate
U S Ra l ad Men	5	12 7	9	19 6	11	20 0	6	12 3
F t Fi la d	8	61 3	3	28 3	12	39 5	4	18 0
t F land	4	27 0	5	24 0	4	12 6	0	0 0
ph n	5	52 4	2	10 3	7	12 9	1	15 6
D lmatia	0	0 0	2	9 6	1	4 0	0	0 0
S nia	0	0 0	4	19 7	6	17 6	2	12 5
K na	1	14 7	3	13 7	0	0 0	0	0 0
M t g o		15 9	3	17 0	3	8 4	0	0 0
C l	4	31 4	2	7 2	7	15 8	4	20 1
R m R lroad M n	4	33 3	0	0 0	0	0 0	1	3 6
t	1	8 0	2	10 4	1	5 3	0	0 0
fu	3	39 7	3	22 5	3	16 2	2	15 1
A l mt ed	37	24 4*	38	15 2*	55	12 7*	20	8 1*

A of th at for all areas

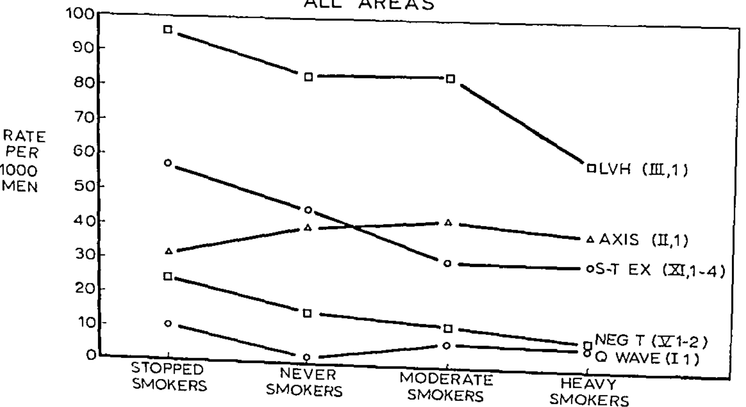

RELATIONSHIP OF ELECTROCARDIOGRAPHIC FINDINGS TO CIGARETTE SMOKING HABIT IN
MEN 40-59
ALL AREAS
RATE PER 1000 MEN
100
90
80
70
60
50
40
30
20
10
0
STOPPED SMOKERS
NEVER SMOKERS
MODERATE SMOKERS
HEAVY SMOKERS
LVH (III,1)
AXIS (II,1)
S-T EX (XI,1-4)
NEG T (V 1-2)
Q WAVE (I 1)

Figure G6

TABLE G8

Frequency (f) of high amplitude R waves left type (Code III 1) in the electrocardiograms of men age 40-59 years by smoking habit class. Rate is age adjusted rate per 1000 men.

AREA	SMOKING HABIT CLASS							
	Stopped Smoking		Never Smoked		Light & Moderate Regular Smokers		Heavy Smokers	
	f	rate	f	rate	f	rate	f	rate
U S Railroad Men	16	35.6	16	3[illegible].5	16	21.8	6	11.7
East Finland	30	210.0	22	184.9	59	193.6	35	135.4
West Finland	23	148.8	33	155.0	63	173.3	18	140.8
Zutphen	2	23.5	5	64.3	29	52.4	2	17.2
Dalmatia	2	19.2	8	39.[illegible]	8	36.4	1	6.1
Slavonia	14	158.8	19	114.9	34	117.3	11	77.1
Velika Krsna	8	146.2	32	156.2	12	163.7	10	145.8
Montegiorgio	5	57.6	2	9.1	15	43.8	2	[illegible].8
Crevalcore	13	109.5	12	47.0	24	58.6	6	36.2
Rome Railroad Men	6	50.8	5	38.3	11	43.3	4	14.5
Crete	7	55.6	8	50.6	12	66.6	8	39.2
Corfu	9	134.1	14	111.5	9	41.0	8	74.4
All areas combined	135	95.8*	176	83.9*	292	84.3*	111	60.1*

* Average of the rates for all areas

TABLE G9

Frequency (f) of negative T waves (Code V 1 2) in the electrocardiograms of men age 40-59 years by smoking habit class. Rate is age adjusted rate per 1000 men

AREA	SMOKING HABIT CLASS							
	Stopped Smoking		Never Smoked		Light & Moderate Regular Smokers		Heavy Smokers	
	f	rate	f	rate	f	rate	f	rate
U S Railroad Men	5	12.7	9	19.6	11	20.0	6	12.3
East Finland	8	61.3	3	28.3	12	39.5	4	18.0
West Finland	4	27.0	5	24.0	4	12.6	0	0.0
Zutphen		52.4	2	10.3	7	12.9	1	15.6
Dalmatia	0	0.0	2	9.6	1	4.0	0	0.0
Slavonia	0	0.0	4	19.7	6	17.6	2	12.5
Velika Krsna	1	14.7	3	13.7	0	0.0	0	0.0
Montegiorgio	2	15.9	3	17.0	3	8.4	0	0.0
Crevalcore	4	31.4	2	7.2	7	15.8	4	20.1
Rome Railroad Men	4	33.3	0	0.0	0	0.0	1	3.6
Crete	1	8.0	2	10.4	1	5.3	0	0.0
Corfu	3	39.7	3	22.5	3	16.2	2	15.[illegible]
All areas combined	37	24.4*	38	15.2*	55	12.7*	20	8.1*

* Average of the rates for all areas

TABLE G10

Frequency (f) of post exercise S-T depression (Code XI, 1-4) in the electrocardiograms of men age 40-59 years by smoking habit class Rate in age-adjusted rate per 1000 men

AREA	SMOKING HABIT CLASS							
	Stopped Smoking		Never Smoked		Light & Moderate Regular Smokers		Heavy Smoke	
	f	rate	f	rate	f	rate	f	rat
U S Railroad Men	23	51 0	33	73 6	23	32 0	19	38
East Finland	5	35 6	2	21 8	7	23 0	5	22
West Finland	4	23 5	7	32 4	14	35 7	4	32
Zutphen	7	91 4	4	40 5	29	52 3	4	43
Dalmatia	1	10 9	3	13 0	3	12 8	1	6
Slavonia	3	28 3	4	22 7	4	12 6	5	36
Velika Krsna	1	15 6	6	27 0	4	25 0	0	0
Montegiorgio	6	66 7	11	67 0	16	42 6	3	47
Crevalcore	4	29 9	11	47 3	15	38 4	6	38
Rome Railroad Men	17	129 3	11	76 7	8	34 1	6	26
Crete	15	114 1	10	49 8	5	26 9	10	48
Corfu	7	92 1	9	73 4	10	45 7	4	36
All areas combined	93	57 4*	111	45 4*	138	31 8*	67	31

* Average of the rates for all areas

TABLE G11

Frequency (f) of large Q waves (Code I 1) in the electrocardiograms of men age 40 59 years by occupational physical activity class Rate is age adjusted rate per 1000 men

AREA	OCCUPATIONAL PH S CAL ACTIVITY CLASS					
	LIGHT		MODERATE		HEAVY	
	f	rate	f	rate	f	rate
U S Railroad Men	13	12 9	13	18 3	-	
East Finland	4	40 2	2	12 4	1	2 2
West Finland	2	29 8	4	33 3	0	0 0
Zutphen	5	19 8	4	8 0	0	0 0
Dalmatia	0	0 0	0	0 0	0	0 0
Slavonia	1	6 4	0	0 0	2	3 6
Montegiorgio	2	36 9	1	4 2	1	1 6
Crevalcore	2	17 0	0	0 0	3	3 9
Rome Railroad Men	1	10 4	1	2 7	2	9 5
Crete	0	0 0	0	0 0	1	2 4
Corfu	1	5 8	1	5 0	1	4 4
All areas combined	31	16 3*	26	7 6*	11	2 8*

* Average of the rates for all areas

Discussion and Conclusions

There is no significant relationship of the prevalence of "infarct" Q waves to cigarette smoking habit among men in these combined areas though non-smokers have the lowest rates

Any possible relationship of left axis deviation with coronary heart disease is apparently independent of smoking habit

There are fewer men with high left type R waves among smokers If this relationship were causal it might be mediated through two other factors associated with habitual heavy cigarette smoking lower average blood pressure and increased obstructive lung disease

Similar explanations can be brought forward for the apparent lower frequency of negative T waves and post-exercise S-T depression in heavy smokers who have lower average blood pressure and relative weight It has not been determined whether an important proportion of heavy cigarette smokers were excluded for clinical cardiac disease from the exercise test However all examined subjects received a resting electrocardiogram

The stopped smokers are the most divergent of all classes and among them are concentrated the highest numbers of infarct Q cases high R waves negative T waves and positive post exercise tests More detailed delineation of this group according to physical characteristics and clinical disease prevalence is indicated The results among stopped smokers are in the opposite direction to that which might be expected from the unusually high ventilatory function values found among men of the same age similarly classified (Blackburn *et al* 1965)

INTER RELATIONS OF ELECTROCARDIOGRAPHIC FINDINGS AND LEVEL OF OCCUPATIONAL PHYSICAL ACTIVITY

Because of interest in the hypotheses concerning physical activity and coronary heart disease we have attempted to analyse here the relationship between five important ECG findings and three reasonable if crude categories of activity according to occupational class among men aged 40 through 59 Though individual areas are analysed results are pooled for all areas combined and age-adjusted rates for ECG items were made from quinquennial rates according to activity class

Large Q Waves (I 1) Table G11 and Figure G7 show the interesting diminution of infarct' Q waves according to increasing activity of the occupation Though the prevalence overall is low the difference is consistent within each age quinquennium as it is in the pooled data The frequencies of large Q waves observed in the three activity classes (sedentary = 16.3 per 1 000 moderate = 7 6 per 1 000 active = 2 8 per 1 000) differ significantly from each other ($p < 003$ *in each case*)

Left Axis Deviation $\geq -30°$ (II 1) Table G12 and Figure G7 indicate no significant relationship between marked abnormal left axis deviation in the ECG and level of activity

High Amplitude R Waves Left Type (III 1) Table G13 and Figure G7 show the stepwise increase of large voltages in the ECG with increasing physical activity of occupation The differences between rates for light (47 1 per 1 000) and those for moderate

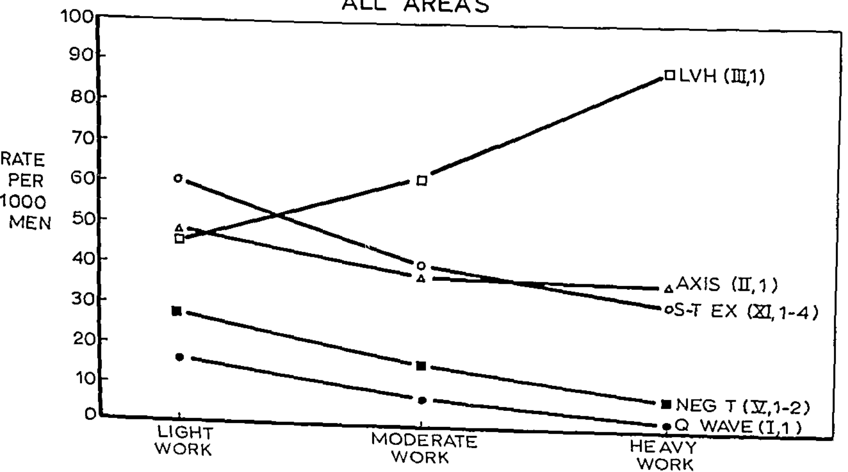

RELATIONSHIP OF ELECTROCARDIOGRAPHIC FINDINGS TO
PHYSICAL ACTIVITY OF OCCUPATION
IN MEN AGED 40-59
ALL AREAS
RATE PER 1000 MEN
100
90
80
70
60
50
40
30
20
10
0
LVH (III,1)
AXIS (II,1)
S-T EX (XI,1-4)
NEG T (V,1-2)
Q WAVE (I,1)
LIGHT WORK
MODERATE WORK
HEAVY WORK

Figure G7

TABLE G12

Frequency (f) of left axis deviation > 30° (Code II 1) in the electrocardiograms of men age 40 59 years by occupational physical activity class Rate is age adjusted rate per 1000 men

AREA	OCCUPATIONAL PHYSICAL ACTIVITY CLASS					
	LIGHT		MODERATE		HEAVY	
	f	rate	f	rate	f	rate
U S Railroad Men	36	37 8	29	24 2		
East Finland	6	61 2	3	20 0	15	26 2
West Finland	3	31 0	10	78 0	27	41 3
Zutphen	12	50 0	20	35 0	3	26 3
Dalmatia	6	96 9	1	8 9	16	29 1
Slavonia	12	89 4	2	31 2	26	46 7
Montegiorgio	3	35 7	11	54 4	30	70 2
Crevalcore	5	37 8	7	40 7	29	41 4
Rome Railroad Men	5	37 0	18	45 1	10	39 8
Crete	2	49 1	13	59 2	17	39 9
Corfu	2	11 6	5	24 9	3	16 5
All areas combined	92	48 9*	119	38 3*	176	37 7*

* Average of the rates for all areas

TABLE G13

Frequency (f) of high amplitude R waves left type (Code III 1) in the electrocardio grams of men age 40 59 years by occupational physical activity class Rate is age adjusted rate per 1000 men

AREA	OCCUPATIONAL PHYSICAL ACTIVITY CLASS					
	LIGHT		MODERATE		HEAVY	
	f	rate	f	rate	f	rate
U S Railroad Men	29	29 7	23	19 1	-	--
East Finland	7	69 0	15	107 4	124	215 7
West Finland	10	113 2	18	147 0	111	168 6
Zutphen	9	42 2	23	40 6	6	57 6
Dalmatia	0	0 0	3	41 5	16	30 5
Slavonia	11	88 3	8	125 7	60	122 8
Montegiorgio	1	11 9	5	27 5	18	40 0
Crevalcore	6	54 0	4	21 8	45	65 2
Rome Railroad Men	5	36 4	11	33 1	9	36 6
Cret	0	0 0	12	61 7	23	55 7
Corfu	12	73 6	12	59 6	16	98 0
All areas combined	90	47 1*	134	62 3*	428	89 1*

* Average of the rates for all areas

TABLE G14

Frequency (f) of negative T waves (Code V, 1-2) in the electrocardiograms of men age 40-59 years by occupational activity class Rate is age adjusted rate per 1000 men

AREA	OCCUPATIONAL PHYSICAL ACTIVITY CLASS LIGHT f	rate	MODERATE f	rate	HEAVY f	rate
U S Railroad Men	17	17 3	13	10 7	--	--
East Finland	9	91 8	8	57 8	10	18 2
West Finland	5	52 4	3	27 2	5	8 3
Zutphen	7	27 9	8	14 6	1	9 6
Dalmatia	0	0 0	0	0 0	3	4 8
Slavonia	4	26 7	0	0 0	8	13 4
Montegiorgio	1	11 9	3	17 4	4	7 6
Crevalcore	4	32 2	2	11 3	11	14 8
Rome Railroad Men	2	20 8	2	9 2	1	3 8
Crete	0	0 0	2	9 2	2	4 8
Corfu	6	31 6	5	24 3	0	0 0
All areas combined	55	28 4*	46	16 5*	45	8 5*

* Average of the rates for all areas

TABLE G15

Freuqency (f) of post exercise S-T depression (Code XI, 1-4) in the electrocardiograms of men age 40-59 years by occupational physical activity class Rate is age adjusted rate per 1000 men

AREA	OCCUPATIONAL PHYSICAL ACTIVITY CLASS LIGHT f	rate	MODERATE f	rate	HEAVY f	rate
U S Railroad Men	56	59 0	42	35 4	-	--
East Finland	3	36 0	8	61 9	8	13 8
West Finland	6	77 5	4	32 4	19	27 8
Zutphen	15	64 8	25	43 6	4	41 4
Dalmatia	2	31 2	1	8 9	5	7 8
Slavonia	6	50 1	1	16 7	9	17 5
Montegiorgio	6	122 6	13	67 7	17	53 0
Crevalcore	5	37 0	10	58 0	21	32 7
Rome Railroad Men	10	70 9	9	24 9	8	37 3
Crete	3	58 4	13	57 9	24	55 7
Corfu	10	63 6	10	47 8	10	59 0
All areas combined	122	61 0*	136	41 4*	125	32 6

* Average of the rates for all areas

(62 3 per 1 000) workers are statistically significant (d = 15 2 S E = 6.52 p < 02) as is that between heavy (89 1 per 1 000) and moderate workers (d = 26 8 S E = 6 13 p < 0001) The difference exists within each 5 year age class

Negative T Waves (V 1—2) Table G14 and Figure G7 show the regular decrease in prevalence of important negative T waves among men in occupations involving light (28 4 per 1 000) moderate (16 5 per 1 000) and heavy (8 5 per 1 000) physical activity The difference in prevalence rate between light and moderate activity classes (S E = 4 04 p = 003) and *between moderate and heavy activity classes (S E = 2 50 p = 001) are* both statistically significant The association is principally due to the findings in the decade 50—59 years

Post exercise S T Depression (XI 1—4) Table G15 and Figure G7 indicate the consistent reduction in post-exercise S T depressions all types among men of all areas with increasing habitual physical activity of occupation If anything the prevalence among sedentary men is underestimated since they are more likely than the average to be excluded for disabilities from the standard work test

Though the difference in prevalence between light (61 0 per 1 000) and moderate (41 4 per 1 000) workers is clearly significant statistically (d = 19 6 S E = 3 23 p = 001) and that between moderate and heavy (32 6 per 1 000) is only of doubtful significance (d = 0 8 S E = 4 30 p = 05) the trends are consistent throughout the detailed analyses by quinquennial age class

Discussion and Conclusions

If large Q waves so defined (I 1) represent in fact a core of well established coronary cases (infarction) the relationship seen here between prevalence of coronary disease and activity habit is impressive However it must be recalled that several influences tend to concentrate prevalence of this disease in sedentary classes in cross-sectional surveys including retirement and job change due to illness (Taylor *et al* 1964) Most of this bias is eliminated but possibly not all in the mode of sampling interrogation and classification used in these studies

Left axis deviation of severe degree is not influenced by activity class though there are leftward trends of QRS axis observable among athletes (Rautaharju 1958)

Clearly the left ventricular mass crudely reflected in high voltages at specified surface leads (Code III 1) would appear to be associated with the habitual occupation of middle-aged men The finding cannot be adequately explained by differences in body build or the absence of insulating subcutaneous fat among the heavy workers

The same factors concentrating "coronary cases' (infarct Q waves I 1) *among sedentary workers and the same* likelihood of this being an inadequate explanation of the differences found may apply to the excess of non specific T *and post-exercise S-T findings* among these men All three coronary-related ECG findings show relationships with occupation as strong as those *found with arterial pressure and much* more significant associations than those found on cross-sectional analysis with serum cholesterol level and smoking habit

H GRADES OF OBESITY AND HYPERCHOLESTEROLEMIA — PRACTICAL STANDARDS

For many purposes it is desirable to classify men with respect to body fatness and serum cholesterol concentration and to identify grades of obesity and of hypercholesterolemia However acceptable reference standards and norms have been lacking and no reasonable classification system has been seriously proposed for either variable in spite of a large amount of literature and propaganda about the health significance of these characteristics

Various cutting points have been used for the purposes of analyzing the relationship of serum cholesterol level to the incidence of clinical coronary heart disease in follow-up studies in the United States 275 mg per 100 ml (Doyle *et al* 1957) 260 (Dawber *et al* 1957) 221 (Keys *et al* 1963) 256 (Paul *et al* 1963) 270 (Chapman and Massey 1964) Many opinions have been hazarded about the "normal range" or "upper limit of normality" for serum cholesterol insofar as these have any real basis they mainly relate to findings not properly analyzed statistically on non-random samples of so-called "healthy" people in particular populations that are not necessarily characterized by desirable distributions of this variable In the United States the most commonly cited "range of normality' is 150—250 mg cholesterol per 100 ml (see e g Hepler 1951 Damm 1965) but evidence to support these figures is not offered As for obesity not even such poorly based guidance has been offered the erroneous identification of relative body weight with obesity is an unacceptable substitute which has created much confusion

In most relatively developed countries both serum cholesterol and body fatness (measured by skinfolds or other objective criteria of actual fat in the body) are age-related tending to rise from youth to reach a maximum in middle age Further at any given age high values for these variables are associated with increased risk of coronary heart disease and reduced life expectancy (Technical Group 1956 Dawber *et al* 1959 Doyle *et al* 1959 Keys *et al* 1963 Paul *et al* 1963 Chapman and Massey 1964) Standards proposed for these variables should reflect these considerations if they are to be applied in health guidance Obviously it is undesirable to use standards based solely on distributions of these variables in populations in which obesity and high levels of serum cholesterol are unduly common and are associated with an unfavorable disease frequency

The data in the present series of studies would seem to provide suitable bases with numbers adequate for statistical treatment for classification systems for obesity and hypercholesterolemia in

middle aged men The sum of the skinfold thicknesses (over the triceps and over the tip of the scapula) is a suitable indicator easily measured of body fatness or obesity The samples are strictly representative only of the populations selected for study but there is no reason to suggest that these populations are peculiar or that the samples are not reasonably representative of populations who are currently "healthy

Over the age range of 40 through 59 years there are, in general no important age trends in either Σ skinfolds or serum cholesterol in this material Isolated exceptions are tendencies for the oldest (55—59) U S switchmen to have higher serum cholesterol values than at younger ages and in Crete for relative obesity to become more and more rare with advancing age Accordingly for many purposes it is acceptable to group all men aged 40—59 in each sample

Bases for Classification — Choice of Samples

The combined data from all samples of men studied could be used as the basis for a proposed classification in regard to obesity and hypercholesterolemia and as will be seen one set of calculations was made on this basis However the examination findings as well as vital statistics suggest separation of the samples into two categories the men in Finland the Netherlands and in the U S A (Group A) and the men in Greece Italy and Yugoslavia (Group B) Further it seemed wise to omit for these purposes the data from Japan and Nicotera (because of some questions as to comparability of ECG data) and from the Rome railway men (because of questions about the sample)

Table H1 summarizes death rates from the sum of all causes in 1961 (data compiled by the World Health Organization) and prevalence rates of ECG abnormalities in the samples studied The death rate averages were computed as unweighted averages of the rates for the countries concerned and also as weighted averages using the figures for population of men of specified age in each country Whichever average is used among men of these ages the death rates are substantially lower in Group B countries than in Group A Using the unweighted averages for all ages 40—59 the Group A rate is 127 9 per cent of the Group B rate, for weighted averages the rate is 123 5 per cent

In the samples studied the prevalence of ECG evidence of definite or possible coronary heart disease is about twice as high in Group A as in Group B countries For major Q waves (Code I 1) the unweighted averages for the four 5-year age classes are 9 98 per 1 000 men in Group A 4 03 in Group B countries this difference is highly significant (chi square = 8 882 p = 0 002) If we add to these prevalences those for T inversion or S-T depression in rest the rates are 32 9 per 1 000 men in Group A and 17 4 in Group B this difference is even more highly significant

Norms for Σ Skinfolds and Serum Cholesterol Classes

Figure H1 shows the Σ skinfold distributions (on a probability scale) for all 18 samples of men and for the samples of men in rural Italy Yugoslavia and Greece ("Group B" countries) Figure H2 similarly shows the distributions of serum cholesterol values These graphs allow easy selection of appropriate cutting points to define grades of obesity and hypercholesterolemia

TABLE H1

Comparison of men of specified age in GROUP A countries (Finland, Netherlands, U S A white) and in GROUP B countries (Greece Italy Yugoslavia) Death rates (1961) from all causes (per 100 000) and prevalence of specified E C G abnormalities Values for ages 40-59 are unweighted averages of values for the quinquennial age groups

COUNTRIES	ITEM	40-44	45-49	50-54	55-59	40 59
Group A	Death rate unweighted av	401	646	1071	1674	948
" B	" " " "	322	493	814	1343	743
Group A	Death rate population weighted av	402	670	1123	1702	974
" B	" " " " "	334	526	875	1441	794
Group A	No men in samples studied	1080	1076	1175	1156	4487
" B	" " " " "	897	1312	1399	1187	479[illegible]
Group A	Old infarcts/1000	7 4	7 5	9 4	15 6	10 0
" B	" " "	0	2 3	7 1	6 7	4 0
Group A	Infarcts + cases T ST abnormal/1000	26 8	29 8	28 1	46 7	32 9
" B	" " " " " " "	10 0	18 8	20 7	20 2	17 4

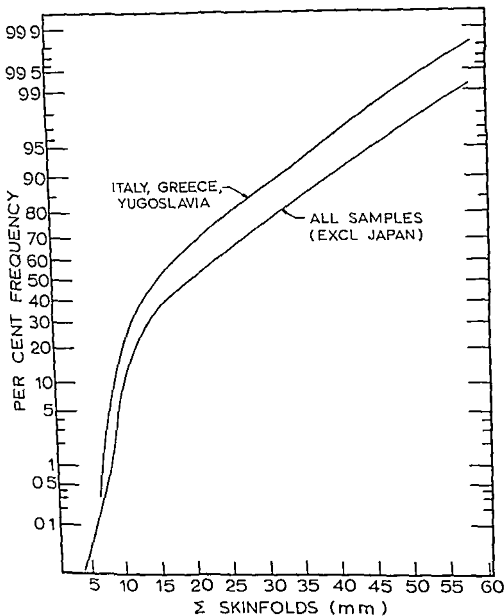

99 9
99 5
99
95
90
80
70
60
50
40
30
20
10
5
1
0 5
0 1
PER CENT FREQUENCY
ITALY, GREECE, YUGOSLAVIA
ALL SAMPLES (EXCL JAPAN)
5 10 15 20 25 30 35 40 45 50 55 60
Σ SKINFOLDS (mm)

Figure H1

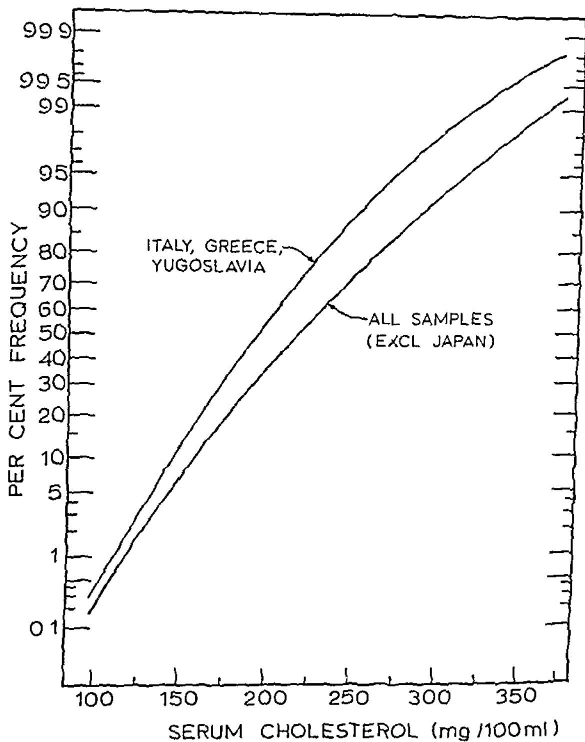

99 9
99 5
99
95
90
80
70
60
50
40
30
20
10
5
1
0 1
PER CENT FREQUENCY
ITALY, GREECE, YUGOSLAVIA
ALL SAMPLES (EXCL JAPAN)
100
150
200
250
300
350
SERUM CHOLESTEROL (mg /100ml)

Figure H2

TABLE H2

Classifications of obesity and hypercholesterolemia based on distributions of men in all samples excluding Japan and Nicotera (A + B) and in Greece Italy and Yugoslavia excluding Rome railway men and Nicotera (B)

CLASSIFICATION	OBESITY SKINFOLDS Range (mm)	OBESITY % of MEN in Range	HYPERCHOLESTEROLEMIA CHOLESTEROL Range (mg /100)	HYPERCHOLESTEROLEMIA % of MEN in Range
A+B)				
1 Severe	over 45	4 8	over 310	4 7
2 Marked	40 45	4 8	291-310	4 3
3 Moderate	36 39	5 2	276 290	5 0
4 Slight	33-35	5 2	261 275	6 8
B)				
1 Severe	over 37	4 9	over 270	4 9
2 Marked	32 37	5 2	251 270	[illegible] 3
3 Moderate	29 31	4 1	241 250	4 3
4 Slight	26 28	5 4	231-240	5 2

TABLE H3

Percentages of men who exceed specified values for Σ skinfolds and for serum cholesterol Values specified are those above which are found 20% 15% 10% and 5% of men in the combined distribution of low risk areas

SAMPLE	Σ Skinfolds (mm) over 25	28	31	37	Serum Cholesterol mg % over 230	240	250	270
1 U S Switchmen	67	58	48	29	55	46	38	24
2 U S Sed Clerks	76	66	54	33	55	46	38	24
3 U S Non Sed Clerks	71	62	55	38	54	47	42	25
4 U S Executives	77	69	59	39	60	53	45	22
5 East Finland	16	12	9	5	73	67	60	46
6 West Finland	20	15	11	7	68	60	52	36
7 Zutphen	42	32	22	10	50	41	32	19
8 Dalmatia	16	12	8	3	16	10	6	3
9 Slavonia	17	13	10	5	22	17	12	5
10 Crevalcore	39	31	25	13	22	17	11	6
11 Montegiorgio	16	10	7	4	21	16	11	6
12 Crete	13	9	6	2	27	20	15	7
13 Corfu	16	12	9	4	24	18	13	6
14 Velika Krsna	7	5	2	1	2	1	0	0
15 Rome Railroad Men	51	41	32	18	28	21	15	7
16 Tanushimaru	8	5	3	2	19	16	13	9
17 Ushibuka					1	0	0	0
18 Nicotera	16	12	8	5	12	6	3	0
Mean Lines 1 7	53	45	37	23	59	51	44	28
Mean Lines 8 14	18	13	10	5	19	14	10	5
Mean Lines 1 18	33	27	22	13	34	28	23	14

If the top 20 per cent of the distribution is considered to represent obesity or hypercholesterolemia, grades may be assigned Grades 1 2 3 and 4 are the 80th to the 84th centiles 85th to 89th 90th to 94th and 95th or over Descriptive terms may be applied to these cuts 'slight' 'marked' 'severe' and 'extreme' respectively Table H2 gives these cutting points for all samples combined and for the six samples in Group B countries

In view of the superiority of the Group B countries in death rates and in ECG findings it seems proper to advocate the B classification system in questions concerning "health" and risk of death or coronary heart disease at these ages Table H3 shows the prevalence of obesity and of hypercholesterolemia, with this classification in each of the samples studied

APPENDIX

If the top 20 per cent of the distribution is considered to represent obesity or hypercholesterolemia, grades may be assigned Grades 1 2 3 and 4 are the 80th to the 84th centiles 85th to 89th 90th to 94th and 95th or over Descriptive terms may be applied to these cuts 'slight' 'marked', 'severe' and 'extreme', respectively Table H2 gives these cutting points for all samples combined and for the six samples in Group B countries

In view of the superiority of the Group B countries in death rates and in ECG findings it seems proper to advocate the B classification system in questions concerning "health" and risk of death or coronary heart disease at these ages Table H3 shows the prevalence of obesity and of hypercholesterolemia, with this classification in each of the samples studied

VIII TRANSPORTATION CONT

49 Railroad dispatcher station master
50 Railroad engineer fireman
51 Railroad maintenance of way
52 Railroad switchman
53 Sailor (not officer)

IX BUILDING TRADES

16 Building trades foreman
54 Bricklayer
54 Mason stone mason stone cutter stone worker
55 Builder general
56 Cabinet maker joiner
56 Carpenter finish
57 Carpenter general
58 Cement worker
58 Plasterer
59 Electrician
60 Painter
61 Plumber pipe fitter

X METAL WORKER MECHANIC

62 Blacksmith
62 Iron worker
62 Foundryman
63 Engineer stationary
64 Machinist
64 Mechanic general
64 Welder
65 Mechanic auto

XI AGRICULTURE FISHERIES FORESTING

66 Surveyor
66 Agronomist agriculturalist
67 Farmer employee farmhand farmworker fieldhand
68 Farmer manager share cropper
69 Farmer self employed
70 Fisherman
71 Flower grower florist
71 Truck gardener
72 Forester
73 Logger lumberjack
74 Lumberman
75 Herdsman stableman
75 Shepherd

XII MINES

19 Mining foreman
6 Miner underground
77 Mine worker aboveground

XIII FACTORY WORKERS

17 Foreman
78 Light work
79 Moderate work
80 Heavy work

XIV SERVICES

39 Waiter food handler
45 Porter bellman bellhop
71 Gardener
81 Attendant usher
81 Nurse
82 Barber
83 Barman
84 Janitor
85 Servant
86 Soldier (not officer) border guard
87 Street cleaner

XV GENERAL LABOR

51 Roadbuilder maintenance
88 Chimney sweep
88 Laborer common
88 Odd jobs heavy
88 Unskilled laborer workman
89 Quarryman

XVI MISCELLANEOUS

89 Entertainer
90 Odd jobs not heavy
91 Peddler hawker
92 Misc skilled & semi skilled crafts e g locksmith tin smith or sheet metal worker furrier glassblower glazer well driller etc
92 Cooper potter weaver basket maker
93 Student
94 Warehouseman warehouse-worker

XVII NOT OCCUPIED

95 Pensioner retired
96 Beggar
97 Invalid
98 Unemployed

CODES FOR OCCUPATIONS - BY CLASSES

I PROFESSIONAL

1 Architect
1 Engineer (design etc)
2 Artist sculptor
2 Newspaperman
2 Librarian
2 Musician composer
2 Writer
3 Dentist
4 Doctor (M D)
5 Druggist
5 Pharmcist
6 Judge
6 Lawyer
7 Military officer
8 Monk
8 Pastor
8 Priest
8 Rabbi
9 Scientist chemist economist psychologist statistician mathematician physicist
10 Teacher school administrator

II BUSINESS GOVERNMENT OFFICIAL ETC

11 Businessman
11 Executive
11 Manager business not farm
11 Merchant
12 Government official
12 Tax collector assessor
13 Landowner
13 Proprietor employer
13 Shopowner
14 Salesman office or travelling
15 Salesman shop or store

III FOREMAN

16 Building trades
17 Factory
18 Logging and lumber
19 Mining
20 Misc foreman
21 Road and railroad
22 Ship's officer

IV CLERICAL ETC

23 Accountant cashier in bank
24 Clerk stenographer secretary
24 Cashier in store restaurant
24 Postal clerk

IV CLERICAL ETC CONT

24 Railroad clerk
25 Draftsman
26 Telegrapher
26 Telephonist
26 Typist

V PROTECTION ETC

27 Fireman
28 Guard customs agent
28 Policeman
29 Postman mailman
30 Watchman

VI FOOD HANDLER

31 Baker
32 Butcher
33 Candy or pastry maker
34 Cook chef
35 Dairyman cheese maker etc
36 Grocer
37 Miller
38 Restaurant cafe keeper inn keeper coffee house keeper
39 Waiter

VII SKILLED LIGHT CRAFTS

40 Harness maker saddle maker
40 Shoemaker
41 Jeweler
41 Watchmaker watch repair man horologist
42 Photographer
43 Printer bookbinder
43 Tailor
44 Undertaker mortician

VIII TRANSPORTATION

24 Railroad clerk
45 Dock worker
45 Stevedore longshoreman
46 Driver auto bus taxi chauffeur
47 Driver mule horse etc
48 Conductor (railway trolley bus)
48 Railroad conductor brakeman
48 Bus or street car (trolley) conductor

Code No	Occupation
37	Miller
6	Miner, underground
77	Mine worker, aboveground
19	Mining foreman
20	Miscellaneous foreman
92	Miscellaneous skilled and semi skilled crafts*
8	Monk
2	Musician, composer
2	Newspaperman
81	Nurse
88	Odd jobs, heavy
90	Odd jobs, not heavy
12	Official, government
60	Painter
8	Pastor
33	Pastry maker
91	Peddler, hawker
95	Pensioner
5	Pharmacist
42	Photographer
9	Physicist
61	Pipe fitter
58	Plasterer
61	Plumber
28	Policeman
45	Porter
24	Postal clerk
29	Postman, mailman
92	Potter
8	Priest
43	Printer
13	Proprietor
9	Psychologist
89	Quarryman
8	Rabbi
21	Railroad foreman
24	Railroad clerk
48	Railroad conductor, brakeman
49	Railroad dispatcher, station master
50	Railroad engineer, fireman
51	Railroad maintenance of way
52	Railroad switchman
38	Restaurant, cafe keeper, innkeeper, coffee house keeper
95	Retired
51	Road builder, maintenance
2	Road and railroad foreman
40	Saddle maker
3	Sailor (not officer)

Code No	Occupation
14	Salesman, office or travelling
15	Salesman, shop or store
9	Scientist
10	School administrator
24	Secretary
85	Servant
75	Shepherd
21	Ship's officer (foreman)
40	Shoemaker
13	Shopowner
92	Skilled and semi skilled (misc.)*
86	Soldier (ot officer), border guard
9	Statistician
24	Stenographer
45	Stevedore
87	Street cleaner
93	Student
66	Surveyor
43	Tailor
12	Tax collector, assessor
46	Taxi driver
10	Teacher
26	Telegrapher
26	Telephonist
71	Truck gardener
26	Typist
44	Undertaker, mortician
98	Unemployed
88	Unskilled laborer, workman
81	Usher
39	Wa er (food handler)
94	Warehouseman or warehouse worker
41	Watchmaker, watch repairman, horologist
30	Watchman
92	Weaver, basket maker
64	Welder
2	Writ r

Notes

75 Herdsman includes shepherd, goat herd, cowherd, swineherd, stableman, etc.

54 Mason includes stone worker, stone cutter, but no quarryman or cement worker

92 Misc. skilled and semi skilled crafts: locksmith, h nam th or sheet metal worker, furrier, glassblower, glazier, w l driller, etc.

CODES FOR OCCUPATIONS - ALPHABETICAL

Code No	Occupation
23	Accountant
66	Agronomist agriculturalist
1	Architect
2	Artist sculptor
12	Assessor, tax
81	Attendant
31	Baker
82	Barber
83	Barman
96	Beggar
45	Bellman bellhop
62	Blacksmith
43	Bookbinder
54	Bricklayer
55	Builder general
16	Building trades foreman
11	Businessman
32	Butcher
56	Cabinet maker joiner
33	Candy maker
56	Carpenter finish
57	Carpenter, general
23	Cashier bank etc
24	Cashier store restaurant
58	Cement worker
46	Chauffeur
34	Chef
9	Chemist
88	Chimney sweep
24	Clerk
12	Collector tax
48	Conductor (railway trolley bus)
34	Cook
92	Cooper
28	Customs agent
35	Dairyman cheese maker etc
3	Dentist
45	Dock worker
4	Doctor (M D)
25	Draftsman
46	Driver auto bus etc
47	Driver mule horse etc
5	Druggist
9	Economist
59	Electrician
13	Employer
1	Engineer (design etc)
63	Engineer stationary
89	Entertainer
11	Executive
17	Factory foreman
78	Factory, light work
79	Factory moderate work
80	Factory heavy work
67	Farmer employee farmhand
68	Farmer manager share cropper
69	Farmer self-employed
27	Fireman
70	Fisherman
71	Flower grower florist
72	Forester
16	Foreman building trades
17	Foreman factory
18	Foreman logging and lumber
19	Foreman mining
20	Foreman miscellaneous
21	Foreman road and railroad
62	Foundry man
71	Gardener
12	Government official
36	Grocer
28	Guard
40	Harness maker
75	Herdsman stableman*
38	Inn keeper
97	Invalid
62	Iron worker
84	Janitor
41	Jeweler
56	Joiner
6	Judge
88	Laborer common
13	Landowner
6	Lawyer
2	Librarian
73	Logger lumberjack
18	Logging and lumber foreman
45	Longshoreman
74	Lumberman
64	Machinist
11	Manager business not farm
68	Manager farm
54	Mason*
9	Mathematician
65	Mechanic auto
64	Mechanic general
11	Merchant
7	Military officer

THE ELECTROCARDIOGRAPHIC CODE

The prevalence data from all areas were coded systematically by the classification to follow Attention is directed to the small modification found here from the original published code (Blackburn Keys et al 1960) under items IV and XI Junctional type S-T depression was thereby segregated from ischemic type Subsequent revision of the code along with greater details of coding procedure is to be found in Rose and Blackburn (1965)

Findings are reported only when they appear in the designated leads (listed on the right hand side of the classification below) I II V_2 V_6 means any of leads I II $V_{2\ 3\ 4}$ 5 or 6 V_1 through V_4 means all of leads V_1 through V_4 A positive finding in any of the designated leads is reportable unless the classification stipulates otherwise Within each major category (Roman Numeral) only the most significant deviation is reported (generally the lowest Arabic Numeral) A finding which meets a criterion in a single complex only and therefore might be an artifact or expression of beat-to beat variation is not to be reported as positive Standardization is 1 cm 1 mv

CODE FOR RESTING ELECTROCARDIOGRAMS

CO	PUNCH	CATEGORY	LEADS
1	0	NO HEREIN REPORTABLE ECG ITEMS I VIII INCLUSIVE	
		Q AND QS PATTERNS (Q must be 1 mm or more with associated R of 1 mm or more)	
	1	CLASS I (any of a through g)	
		a Q/R 1/3 or more and Q duration 0 03 sec or more	I II V_2 V_6
		b Q duration 0 04 sec or more	I II V_1 V_6
		Q duration 0 04 sec or more and R amplitude 3 mm or more	aVL
		d Q duration 0 05 sec or more and a Q wave present in aVF	III
		Q duration 0 05 sec or more	aVF
		f QS pattern when R wave is present in adjacent or coronal lead to the right	V_2 V_6
		g QS pattern	V_1 through V_4
			V_1 through V
			V_1 through V_6
			I II V_2 V_6
			I II V_2 V_6
			aVL
			III
			aVF
			III aVF

SMOKING CLASSIFICATION CODES

Card Col	Punch	Cigarettes
36	0	Never
	1	Stopped < 1 yr
	2	Stopped 1-9 yrs
	3	Stopped 10 or more yrs
	4	Now < 5/day
	5	Now 5-9/day
	6	Now 10-19/day*
	7	Now 20-29/day
	8	Now 30 or more/day

Card Col	Punch	Pipefuls
37	0	Never
	1	Stopped < 1 yr
	2	Stopped 1-9 yrs
	3	Stopped 10 or more yrs
	4	Now < 3/day
	5	Now 3-4/day
	6	Now 5-9/day
	7	Now 10-19/day
	8	Now 20 or more/day

Card Col	Punch	Cigars
38	0	Never
	1	Stopped < 1 yr
	2	Stopped 1-9 yrs
	3	Stopped 10 or more yrs
	4	Now < 2/day
	5	Now 2-4/day
	6	Now 5-7/day
	7	Now 8 or more/day

Card Col	Punch	Formerly
39	0	< 5 cigs /day
	1	5-9 cigs /day
	2	10-19 cigs /day
	3	20-29 cigs /day
	4	30 or more cigs /day
	5	Light pipe no cigs
	6	Heavy pipe no cigs
	7	Light cigar, no cigs
	8	Heavy cigar, no cigs
	9	Pipe + Cigar no cigs

* Classifications applicable to U S Railroad samples are similar to these though slightly less refined Note however that for U S Railroad samples the upper limit for moderate cigarette smokers is 20 cigarettes per day rather than 19 as indicated above

COL	PUNCH	CATEGORY	LEADS
	4	S T J depression of 1 mm or more and S T segment upward sloping	I II aVL aVF V_1 V_6
V		T WAVE ITEMS	
	1	T amplitude minus 5 mm or more	I II V_2 V_6
		when R amplitude 5 mm or more	aVL
		when QRS mainly upright	aVF
	2	T amplitude minus 1 to 5 mm	I II V_2 V_6
		when R amplitude 5 mm or more	aVL
		when QRS mainly upright	aVF
	3	T wave flat or small diphasic (negative phase less than 1 mm)	I II V_3-V_6
		when R amplitude 5 mm or more	aVL
		when QRS mainly upright	aVF
VI		A V CONDUCTION	
	1	Complete A V block (permanent or intermittent)	any
	2	Partial A V block	any
	3	P R interval over 0 21 sec (any heart rate)	I II III
	4	Accelerated conduction (Wolff Parkinson White)	any
VII		VENTRICULAR CONDUCTION	
	1	Left bundle branch block (LBBB)	
		QRS duration 0 12 sec or greater in	I II III
		and R peak duration 0 06 sec or more in any of	I II aVL V_5 V_6
	2	Complete right bundle branch block (RBBB)	
		QRS duration 0 12 sec or greater in	I II III
		and R prime greater than R in	V_1
	3	Incomplete RBBB R prime greater than R and QRS duration less than 0 12 sec	V_1
		(report under III 2 if those criteria are met)	
	4	Intraventricular block QRS 0 12 sec or more and no LBBB or RBBB pattern	I II III
VIII		ARRHYTHMIAS	
	0	Any combination of arrhythmias below	
	1	Frequent (10 per cent or more of recorded beats) premature auricular nodal or ventricular beats	
	2	Ventricular tachycardia (over 100/min)	
	3	Atrial fibrillation or flutter	
	4	Supra ventricular tachycardia	
	5	Ventricular (idioventricular) rhythm (up to 100/min.)	
	6	A V nodal rhythm (up to 100/min)	
	7	Sinus tachycardia (over 100 /min)	
	8	Sinus bradycardia (under 50/min)	
	9	Arrhythmias not mentioned above	

CODE FOR POST EXERCISE ELECTROCARDIOGRAMS

COL	PUNCH	CATEGORY
X		EXERCISE TEST
	1	No exercise test made
	2	Exercise test stopped

COL	PUNCH	CATEGORY	LEADS
		g QS pattern and absence of Code VII_1	V_1 through V_3
		h Decreasing absolute R amplitude <u>and</u> smallest R = 2 mm or less <u>and</u> absence of Code III_2 or $VII_{2\ 3}$	V_1 through V_3 V_4
		i Q duration = 0 04 sec or more or a QS pattern	(Ancillary leads see text)
	3	CLASS III (any of a through c)	
		a Q/R = 1/3 or more <u>and</u> Q duration less than 0 03 sec	I II V_2-V_6
		b QS pattern <u>and</u> absence of Code VII_1 or III_1	V_1 and V_2
		c Q/R = 1/5 to 1/3 <u>and</u> Q duration less than 0 03 sec	I II V_2-V_6
II		*QRS AXIS DEVIATION*	
	1	Left QRS axis = -30° or greater	I II and III
	2	Right QRS axis = +120 or greater (The algebraic sum of major positive and major negative waves must be negative in I positive in III and in I must be one half or more of that in III)	I II and III
III		HIGH AMPLITUDE R WAVES	
	1	Left R more than 26 mm	V_5 V_6
		R more than 20 mm	I, II III aVF
		R more than 12 mm	aVL
	2	Right QRS duration less than 0 12 sec <u>and</u> R amplitude = 5 mm or more <u>and</u> R/S ratio = 1 0 or more <u>and</u> QRS transition zone or decreasing R/S to left of V_1 (Includes incomplete RBBB which meets above criteria)	V_1
IV		S-T JUNCTION AND SEGMENT (Measured from preceding P-R interval at onset of QRS)	
		Depression	
	1	S-T-J depression of 1 mm or more and S-T segment horizontal or downward sloping	I II aVL aVF V_1 V_6
	2	S-T-J depression 0 5 0 9 mm and S T segment horizontal or downward sloping	I II aVL aVF V_1-V_6
	3	No S-T-J depression as must as 0 5 mm but S-T segment sloping down and reaching 0 5 mm or more below P-R baseline	I II aVL aVF V_1-V_6

COL	PUNCH	CATEGORY
	3	Change from no coded ventricular conduction item at rest to incomplete right bundle branch block
	4	Change from no coded ventricular conduction item at rest to intraventricular block
	5	Change from one coded ventricular conduction item at rest (VII 1 4) to another ventricular conduction item post exercise
	6	No change from resting coded ventricular conduction item
	7	Change from any ventricular conduction item at rest (VII 1-4) to no ventricular conduction item post exercise
XV		ARRHYTHMIAS POST-EXERCISE (exclude VIII 7-8 sinus tachy and bradycardia)
	1	Change from no coded arrhythmia at rest to any reportable arrhythmia post exercise
	2	Change from one coded arrhythmia at rest to another arrhythmia post-exercise
	3	No change from coded resting arrhythmia
	4	Change from any arrhythmia at rest to no arrhythmia post-exercise

PUNCH	CATEGORY
	S-T ITEMS POST-EXERCISE
1	Change from no coded S-T item at rest to S-T item Type IV 1 post-exercise
2	Change from no coded S-T item at rest to S-T item Type IV 2 post-exercise
3	Change from no coded S-T item at rest to S-T item Type IV 3 post-exercise
4	Change from no coded S-T item at rest to S-T item Type IV 4 post-exercise
5	Change from one coded S-T item at rest to a lower numerical S T item post-exercise (IV 3 to Type IV, 1 etc)
6	Change from one coded S-T item at rest to a higher numerical item post-exercise (IV, 1 to Type IV 3, etc)
7	No change from resting coded S-T item
8	Change from any coded S-T item at rest to no reportable S-T item post-exercise
9	Questionable S-T depression post-exercise due to technical considerations
	T ITEMS POST-EXERCISE
1	Change from no coded T item at rest to T item Type V 1 post-exercise
2	Change from no coded T item at rest to T item Type V 2 post-exercise
3	Change from no coded T item at rest to T item Type V 3 post-exercise
4	Change from one coded T item at rest to a lower numerical T item post-exercise (V 3 to Type V 2 etc)
5	Change from one coded T item at rest to a higher numerical T item post-exercise (V 2 to Type V 3 etc)
6	No change from resting coded T item
7	Change from any coded T item at rest to no reportable T item post-exercise
8	Questionable T item post-exercise due to technical considerations
	A-V CONDUCTION POST-EXERCISE
1	Change from no coded A-V conduction item at rest to complete A-V block post-exercise
2	Change from no coded A-V conduction item at rest to partial A-V block post-exercise
3	Change from no coded A-V conduction item at rest to P-R interval more than 0 21 sec post-exercise
4	Change from no coded A-V conduction item at rest to accelerated conduction
5	Change from one coded A-V conduction item at rest (VI 1-4) to another A-V condution item post-exercise
6	No change from resting coded A-V conduction item
7	Change from any A-V conduction item at rest to no A-V conduction item post-exercise
	VENTRICULAR CONDUCTION POST-EXERCISE
1	Change from no coded ventricular conduction item at rest to left bundle branch block (LBBB)
2	Change from no coded ventricula conduction item at rest to

Ht.	20 YEARS		21 YEARS		22 YEARS		23 YEARS		24 YEARS	
cm.	0	5	0	5	0	5	0	5	0	5
155	54 0	54 3	54 5	54 8	54 9	55 2	55 4	55 6	55 8	56 1
156	54 5	54 8	55 0	55 3	55 5	55 7	55 9	56 2	56 4	56 6
157	55 1	55 4	55 5	55 8	56 0	56 3	56 4	56 7	56 9	57 1
158	55 6	55 9	56 1	56 3	56 5	56 8	57 0	57 2	57 4	57 7
159	56 1	56 4	56 6	56 8	57 1	57 3	57 5	57 7	57 9	58 2
160	56 7	56 9	57 1	57 5	57 6	58 0	58 0	58 4	58 5	58 9
161	57 2	57 4	57 8	58 2	58 3	58 7	58 7	59 1	59 2	59 6
162	57 7	58 0	58 5	58 9	59 0	59 4	59 4	59 8	59 9	60 3
163	58 3	58 6	59 2	59 6	59 7	60 1	60 2	60 6	60 6	61 0
164	59 0	59 4	60 0	60 4	60 4	60 8	60 9	61 3	61 4	61 7
165	59 7	60 1	60 7	61 1	61 2	61 6	61 6	62 0	62.0	62 4
166	60 4	60 8	61 4	61 8	61 9	62 3	62 3	62 7	62 8	63 2
167	61 2	61 6	62 2	62 5	62 6	62 9	63 1	63 4	63 5	63 8
168	61 9	62 3	62 8	63 0	63 2	63 5	63 7	63 9	64 1	64 3
169	62 6	63 0	63 3	63 5	63 8	64 0	64 2	64 5	64 6	64 9
170	63 3	63 7	63 8	64 2	64 3	64 7	64 8	65 1	65 2	65 5
171	64 0	64 4	64 5	64 9	65 0	65 4	65 4	65 8	65 8	66 2
172	64 8	65 1	65 2	65 6	65 7	66 1	66 2	66 5	66 6	67 0
173	65 4	65 8	65 9	66 3	66 4	66 8	66 8	67 2	67 3	67 7
174	66 2	66 6	66 6	67 0	67 1	67 5	67 6	68 0	68 0	68 4
175	66 9	67 3	67 3	67 7	67 8	68 2	68 3	68 7	68 7	69 1
176	67 6	68 0	68 1	68 5	68 6	69 0	69 0	69 4	69 4	69 8
177	68 3	68 7	68 8	69 2	69 3	69 7	69 8	70 2	70 2	70 6
178	69 0	69 4	69 5	69 9	70 0	70 4	70 5	70 9	70 9	71 3
179	69 8	70 2	70 2	70 6	70 8	71 2	71 2	71 6	71 6	72 0
180	70 5	70 9	71 0	71 4	71 5	71 9	71 9	72 3	72 4	72 8
181	71 3	71 7	71 8	72 2	72 3	72 7	72 8	73 2	73 2	73 6
182	72 -	72 6	72 7	73 1	73 2	73 6	73 6	74 0	74 0	74 4
183	73 1	73 5	73 6	74 0	74 0	74 4	74 5	74 9	74 9	75 5
184	74 0	74 4	74 4	74 8	74 9	75 3	75 4	75 8	76 0	76 6
185	74 8	75 2	75 3	75 7	75 8	76 2	76 2	76 7	77 2	77 7
186	75 7	76 1	76 2	76 7	76 6	77 1	77 2	77 8	78 2	78 7
187	76 6	77 1	77 2	77 5	77 6	78 0	78 3	78 9	79 -	79 8
188	77 6	78 0	78 0	78 4	78 4	78 8	79 4	79 8	80 3	80 7
189	78 4	78 8	78 9	79 3	79 3	79 7	80 2	80 7	81 2	81 6
190	79 3	79 7	79 8	80 2	80 2	80 6	81 2	81 5	82 0	82 5
191	80 2	80 7	80 7	81 1	81 1	81 5	82 0	82 5	83 0	83 4
192	81 1	81 6	81 6	82 0	82 0	82 4	83 0	83 4	83 8	84 2
193	82 0	82 5	82 5	82 9	82 9	83 3	83 8	84 3	84 7	85 2
194	83 0	83 4	83 4	83 8	83 8	84 3	84 8	85 2	85 6	86 1

"STANDARD" AVERAGE RELATIVE BODY WEIGHT

The following table was used for calculating the relative body weights for the men in all samples It is based on the table of average weights for height and age resulting from the Medico-Actuarial Mortality Investigations (Association, 1912, Davenport, 1923), reproduced in many places and sometimes improperly referred to as "Davenport's Table" (see Keys and Brozek 1953, pp 250-256)

The original tabular values in English units converted to the metric system, were graphed and the lines smoothed by hand Interpelations and some small extrapolation were made where necessary

As applied here, the tabular values refer to height without shoes, and weight wearing only light underclothing Values in the body of the table are weights in kilograms for height in steps of 0 5 cm

Ht	30 31 YRS		32 33 YRS		34 35 YRS		36 37 YRS		38 39 YRS	
cm	0	5	0	5	0	5	0	5	0	5
155	58 5	58 7	58 8	59 0	59 0	59 2	59 4	9 6	59 9	60 1
156	58 9	59 1	59 1	59 3	59 3	59 5	59 8	60 0	60 2	60 4
157	59 2	59 4	59 5	59 7	59 7	59 9	60 2	60 4	0 6	60 8
158	59 7	59 9	59 9	60 2	60 1	60 [illegible]	60 6	60 9	61 0	61 3
159	60 2	60 5	60 6	60 7	60 7	60 9	61 2	61 4	61 5	61 8
160	60 2	60 8	60 8	61 0	61 2	61 5	61 7	62 1	6 1	62 4
161	61 1	61 4	61 3	61 6	61 8	62 1	62 3	62 7	62 6	62 9
162	61 7	62 0	61 9	62 2	61 4	62 7	63 0	63 3	63 2	63 5
163	62 3	62 7	62 5	62 9	63 0	63 4	63 7	64 0	63 8	64 [illegible]
164	63 0	63 5	63 2	63 6	63 7	64 1	64 4	64 8	64 6	64 9
165	63 7	64 0	63 9	64 3	64 4	64 8	65 1	65 4	65 3	65 6
166	64 4	64 8	64 6	65 0	65 1	65 5	65 8	66 1	66 0	66 3
167	65 1	65 4	65 3	65 7	65 8	66 1	6 5	6 8	6 7	67 0
168	65 8	66 1	66 0	66 4	66 5	66 9	2	67 5	67 4	67
169	66 5	66 8	66 8	67 1	67 2	67 5	67 9	68 2	68 1	68 4
1 0	67 2	67 5	67 5	67 8	67 9	68 3	68 6	69 0	68 8	69 2
171	67 9	68 2	68 2	68 7	68 7	69 2	69 4	69 9	69 6	0 1
172	68 6	68 9	69 2	69 6	69 6	70 1	70 3	70 8	70 5	1 0
173	69 2	69 6	70 1	70 5	70 5	71 0	1 2	71	71 4	71 8
1 4	70 0	70 3	70 9	71 3	1 4	1 9	2 1	72 5	72 3	72 7
1 5	0 7	71 1	71 7	72 1	72 3	2 7	73 0	73 4	73 2	73 6
176	71 5	72 0	72 5	73 0	73 2	73 6	74 4	74 3	4 1	74 5
177	72 4	72 9	73 4	73 7	74 1	74 5	74 8	5 2	5 0	75 4
178	73 2	73 8	74 3	74 8	5 0	75 4	75 7	76 1	5 9	6 4
179	4 3	74 7	75 3	75 7	75 8	6 3	76 6	7 0	77 0	7 5
180	75 2	5 7	76 1	76 6	6 8	77 2	7 5	77 9	78 1	78 6
181	76 2	76 7	77 1	77 6	77 8	78 3	78 5	9 0	9 2	79 7
182	77 2	77 8	78 1	78 7	8 8	79 4	9 5	80 1	80 2	80 8
183	78 3	8 9	79 5	79 7	79 9	80 5	80 2	81 2	81 3	81 9
184	79 4	9 9	80 3	80 8	81 0	81 5	81 7	82 2	82 4	83 0
85	80 5	81 0	81 4	81 9	82 0	82 6	82 8	83 3	83 5	84 0
186	81 3	82 1	82 4	83 0	83 2	83 8	83 9	84 [illegible]	84 6	85 3
187	82 6	83 1	83 5	84 0	84 4	84 9	85	85 8	85 9	86 5
168	83 6	84 2	84 6	85 1	85 5	86 0	86 4	8 9	87 1	87 6
189	84 7	85 3	85 7	86	86 6	8 1	8 5	88 0	88 2	88 7
190	85 8	86 3	85 7	87 3	87 7	88 7	88 6	89 1	89 4	89 9
191	86 8	87 3	87 8	88 3	88	89 5	89 6	90 1	90 6	91 1
192	87 9	88 4	88 9	89 5	89 8	90 3	90	91 2	91 7	9 2
193	89 1	89 6	90 0	90 6	91 0	91 5	91 4	9 0	92 8	93 3

Ht	25 YEARS		26 YEARS		27 YEARS		28 YEARS		29 YEARS	
cm	0	5	0	5	0	5	0	5	0	5
155	56 3	56 4	56 7	56 9	57 2	57 3	57 6	57 8	58 1	58 3
156	56 6	56 8	57 0	57 2	57 5	57 7	58 0	58 2	58 4	58 6
157	57 0	57 2	57 4	57 6	57 9	58 1	58 1	58 5	58 8	59 0
158	57 4	57 7	57 8	58 1	58 3	58 6	58 8	59 1	59 2	59 5
159	57 9	58 2	58 4	58 7	58 8	59 1	59 3	59 6	59 7	60 0
160	58 5	58 9	59 0	9 4	59 4	59 7	59 9	60 2	60 3	60 6
161	59 2	59 6	59 7	60 1	60 0	60 2	60 4	60 7	60 9	61 2
162	59 9	60 3	60 4	60 8	60 5	60 8	61 0	61 3	61 5	61 8
163	60 6	61 0	61 1	61 5	61 1	61 5	61 6	62 0	62 1	62 5
164	61 4	61 7	61 8	62 2	61 8	62 2	62 4	62 7	62 8	63 2
165	62 0	62 4	62 5	62 9	62 5	62 9	63 0	63 4	63 5	63 8
166	62 8	63 2	63 2	63 6	63 2	63 6	63 8	6 1	64 2	64 6
167	63 5	63 9	64 0	64 3	64 0	64 3	64 5	64 8	64 9	65 2
168	64 2	64 6	64 6	65 0	64 6	65 0	65 2	65 5	65 6	65 9
169	65 0	65 4	65 4	65 8	65 4	65 8	65 9	66 2	66 3	66 6
170	65 7	66 1	66 1	66 5	66 1	66 5	66 6	66 9	67 0	67 3
171	66 4	66 8	66 8	67 2	66 8	67 2	67 3	67 6	67 7	68 0
172	67 1	67 5	67 5	67 9	67 5	67 9	68 0	68 3	68 4	68 7
173	67 8	68 2	68 2	68 6	68 2	68 6	68 7	69 1	69 0	69 4
174	68 5	68 9	68 9	69 3	68 9	69 3	69 4	69 8	69 8	70 1
175	69 2	69 6	69 6	70 0	69 6	70 0	0 2	70 5	70 5	70 8
176	69 9	70 3	70 4	70 7	70 4	70 7	70 8	71 2	71 2	71 6
177	70 6	71 0	71 0	71 4	1 0	71 4	71 6	71 9	72 0	72 3
178	71 4	71 8	71 8	72 2	71 8	72 2	72 3	72 7	2 7	73 2
179	72 3	72 7	72 7	73 1	72 7	73 1	73 2	73 7	73 6	74 1
180	73 2	73 6	73 6	74 0	73 6	74 1	74 1	74 6	74 5	75 0
181	74 0	74 4	74 5	74 9	74 6	75 1	75 1	5 6	75 5	6 1
182	74 9	75 3	75 4	75 9	75 6	76 2	76 1	76 7	76 6	77 1
183	75 8	76 4	6 4	76 9	76 7	77 3	77 2	77 7	77 7	78 2
184	76 9	77 5	77 4	77 9	77 8	78 4	78 3	8 8	8 8	9 3
185	78 0	78 6	8 4	79 0	78 9	79 5	79 3	79 9	79 8	80 4
186	79 1	79 7	79 5	80 1	80 0	80 5	80 4	80 9	80 9	8 5
187	80 2	80 7	80 6	81 1	81 0	81 6	81 5	82 0	82 0	82 5
188	81 2	81 6	81 6	82 2	82 2	82 7	82 5	83 1	83 1	83 6
189	82 1	82 5	82 7	83 3	83 2	83 8	83 6	84	84 1	84 7
190	83 0	83 4	83 8	84 4	84 3	84 8	84	85 3	85 2	85 7
191	83 8	84 2	85 0	85 6	85 3	85 9	85 8	86 3	86 3	86 8
192	84 7	85 1	86 1	86 8	86 4	87 0	86 9	87 4	87 4	87 9
193	85 6	86 1	87 3	88 0			87 5		88 0	
194	86 6	87 0								

TABLE

SWITCHMEN, U S A

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5 10 20, ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
						HEIGHT cm						
40-44	281	164	167	170	172	174	175	177	178	180	184	186
45-49	243	165	168	170	172	173	175	176	178	179	182	184
50-54	152	164	166	168	170	172	174	175	177	179	181	184
55-59	159	164	165	167	169	171	172	174	176	178	180	183
						RELATIVE BODY WEIGHT, Per Cent						
40 44	280	84	88	94	99	102	106	109	114	117	122	126
45-49	243	82	88	92	98	100	103	106	110	114	121	130
50-54	152	84	89	94	99	103	105	109	112	114	119	125
55-59	158	81	86	91	97	102	104	109	111	116	121	128
						SUM OF SKINFOLDS mm						
40-44	281	13	16	21	24	27	31	34	38	41	46	52
45-49	243	14	16	20	23	26	29	32	35	39	45	49
50-54	152	15	20	24	27	30	33	36	39	43	48	54
55-59	159	13	16	20	24	28	32	34	37	42	47	52
						SYSTOLIC BLOOD PRESSURE mm Hg						
40 44	281	110	114	120	124	127	130	134	140	145	157	164
45 49	243	110	113	120	125	129	133	137	143	151	165	171
50-54	153	112	118	123	130	131	136	140	148	158	170	185
55-59	159	116	120	126	130	135	140	149	156	165	175	188
						DIASTOLIC BLOOD PRESSURE 5th Phase mm Hg						
40-44	281	70	71	76	79	80	83	86	88	91	99	102
45 49	243	70	74	77	80	80	84	88	90	95	101	108
50-54	153	71	74	76	80	81	85	89	90	96	105	110
55 59	159	70	73	78	80	83	88	90	93	100	107	112
						SERUM CHOLESTEROL CONCENTRATION mg per 100 ml						
40-44	278	170	183	201	213	225	233	245	256	274	291	320
45-49	239	174	181	199	213	222	232	244	259	274	295	324
50 54	150	192	194	206	218	224	232	244	256	274	294	319
55 59	156	167	190	208	224	236	250	262	273	283	297	319

Ht	40 41 YRS		42-43 YRS		44-45 YRS		46-49 YRS		50 59 YRS	
cm	0	5	0	5	0	5	0	5	0	5
155	60 3	60 5	60 8	61 0	61 3	61 4	61 7	61 9	62 2	62 4
156	60 7	60 9	61 1	61 3	61 6	61 8	62 1	62 2	62 5	62 7
157	61 1	61 2	61 5	61 7	62 0	62 2	62 4	62 6	62 9	63 1
158	61 5	61 8	61 9	62 2	62 4	62 7	62 8	63 1	63 4	63 6
159	62 0	62 3	62 4	62 7	62 9	63 2	63 4	63 6	63 9	64 2
160	62 6	62 9	63 0	63 3	63 5	63 8	63 9	64 1	64 4	64 6
161	63 2	63 4	63 6	63 9	64 1	64 4	64 4	64 7	64 9	65 1
162	63 7	64 0	64 2	64 5	64 7	65 0	65 0	65 3	65 4	65 8
163	64 4	64 7	64 8	65 2	65 3	65 7	65 6	66 0	66 1	66 5
164	65 0	65 4	65 5	65 9	66 0	66 3	66 3	66 7	66 8	67 2
165	65 8	66 1	66 2	66 6	66 7	67 0	67 0	67 4	67 5	67 9
166	66 5	66 8	66 9	67 3	67 4	67 7	67 7	68 1	68 2	68 6
167	67 2	67 5	67 6	68 0	68 0	68 4	68 4	68 8	68 9	69 3
168	67 9	68 2	68 3	68 6	68 7	69 1	69 1	69 5	69 7	70 1
169	68 6	68 9	69 0	69 3	69 4	69 8	69 8	70 2	70 6	71 0
170	69 3	69 7	69 7	70 1	70 1	70 5	70 6	71 0	71 3	71 7
171	70 1	70 5	70 5	71 0	71 0	71 4	71 4	71 8	72 1	72 6
172	71 0	71 5	71 4	71 9	71 9	72 3	72 3	72 7	73 1	73 5
173	71 9	72 4	72 3	72 8	72 8	73 2	73 2	73 7	74 0	74 4
174	72 3	73 3	73 2	73 6	73 7	74 1	74 2	74 6	74 8	75 2
175	73 7	74 1	74 1	74 5	74 6	75 1	75 1	75 5	75 7	76 1
176	74 6	75 0	75 0	75 5	75 5	76 0	76 0	76 4	76 6	77 0
177	75 5	75 9	75 9	76 3	76 4	76 9	76 9	77 3	77 5	77 9
178	76 4	76 9	76 8	77 3	77 3	77 9	77 8	78 3	78 4	78 9
179	77 5	78 1	77 9	78 5	78 4	78 9	78 8	79 4	79 4	79 9
180	78 6	79 1	79 0	79 5	79 4	80 0	79 9	80 5	80 4	80 9
181	79 7	80 2	80 1	80 6	80 5	81 0	81 0	81 5	81 4	81 9
182	80 7	81 3	81 2	81 7	81 5	82 1	82 0	82 6	82 4	83 1
183	81 8	82 4	82 2	82 8	82 6	83 1	83 1	83 7	83 6	84 3
184	82 9	83 4	83 3	83 9	83 7	84 3	84 2	84 8	84 8	85 5
185	84 0	84 5	84 4	84 9	84 8	85 4	85 3	85 9	86 0	86 6
186	85 1	85 7	85 6	86 2	86 0	86 6	86 4	87 0	87 3	87 9
187	86 4	87 0	86 8	87 5	87 2	87 9	87 7	88 3	88 6	89 2
188	87 6	88 2	88 1	88 7	88 5	89 1	88 9	89 5	89 8	90 4
189	88 8	89 4	89 3	90 0	89 7	90 4	90 2	90 8	91 1	91 7
190	90 1	90 7	90 6	91 2	91 0	91 6	91 5	92 1	92 4	93 0
191	91 3	91 9	91 8	92 4	92 2	92 8	92 8	93 4	93 6	94 2
192	92 6	93 1	93 1	93 6	93 4	94 0	94 0	94 7	94 9	95 6
193	93 4	94 0	94 3	94 7	94 8	95 4	95 2	95 8	96 1	96 6

TABLE

SWITCHMEN U S A

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	5	10	20	30	40	50	60	70	80	90	95
						CENTILE						
						HEIGHT, cm						
40 44	281	164	167	170	172	174	175	177	178	180	184	186
45-49	243	165	168	170	172	173	175	176	178	179	182	184
50-54	152	164	166	168	170	172	174	175	177	179	181	184
55 59	159	164	165	167	169	171	172	174	176	178	180	183
						RELATIVE BODY WEIGHT, Per Cent						
40 44	280	84	88	94	99	102	106	109	114	117	122	126
45-49	243	82	88	92	98	100	103	106	110	114	121	130
50 54	152	84	89	94	99	103	105	109	112	114	119	125
55 59	158	81	86	91	97	102	104	109	111	116	121	128
						SUM OF SKINFOLDS mm						
40-44	281	13	16	21	24	27	31	34	38	41	46	52
45-49	243	14	16	20	23	26	29	32	35	39	45	49
50-54	152	15	20	24	27	30	33	36	39	43	48	54
55-59	159	13	16	20	24	28	32	34	37	42	47	52
						SYSTOLIC BLOOD PRESSURE mm Hg						
40 44	281	110	114	120	124	127	130	134	140	145	157	164
45 49	243	110	113	120	125	129	133	137	143	151	165	171
50-54	153	112	118	123	130	131	136	140	148	158	170	185
55-59	159	116	120	126	130	135	140	149	156	165	175	188
						DIASTOLIC BLOOD PRESSURE, 5th Phase, mm Hg						
40-44	281	70	71	76	79	80	83	86	88	91	99	102
45 49	243	70	74	77	80	80	84	88	90	95	101	108
50-54	153	71	74	76	80	81	85	89	90	96	105	110
55 59	159	70	73	78	80	83	88	90	93	100	107	112
						SERUM CHOLESTEROL CONCENTRATION mg per 100 ml.						
40-44	278	170	183	201	213	225	233	245	256	274	291	320
45 49	239	174	181	199	213	222	232	244	259	274	295	324
50-54	150	192	194	206	218	224	232	244	256	274	294	319
55 59	156	167	190	208	224	236	250	262	273	283	297	319

Ht	40-41 YRS		42 43 YRS		44-45 YRS		46-49 YRS		50 59 YRS	
cm	0	5	0	5	0	5	0	5	0	5
155	60 3	60 5	60 8	61 0	61 3	61 4	61 7	61 9	62 2	62 4
156	60 7	60 9	61 1	61 3	61 6	61 8	62 1	62 2	62 5	62 7
157	61 1	61 2	61 5	61 7	62 0	62 2	62 4	62 6	62 9	63 1
158	61 5	61 8	61 9	62 2	62 4	62 7	62 8	63 1	63 4	63 6
159	62 0	62 3	62 4	62 7	62 9	63 2	63 4	63 6	63 9	64 2
160	62 6	62 9	63 0	63 3	63 5	63 8	63 9	64 1	64 4	64 6
161	63 2	63 4	63 6	63 9	64 1	64 4	64 4	64 7	64 9	65 1
162	63 7	64 0	64 2	64 5	64 7	65 0	65 0	65 3	65 4	65 8
163	64 4	64 7	64 8	65 2	65 3	65 7	65 6	66 0	66 1	66 5
164	65 0	65 4	65 5	65 9	66 0	66 3	66 3	66 7	66 8	67 2
165	65 8	66 1	66 2	66 6	66 7	67 0	67 0	67 4	67 5	67 9
166	66 5	66 8	66 9	67 3	67 4	67 7	67 7	68 1	68 2	68 6
167	67 2	67 5	67 6	68 0	68 0	68 4	68 4	68 8	68 9	69 3
168	67 9	68 2	68 3	68 6	68 7	69 1	69 1	69 5	69 7	70 1
169	68 6	68 9	69 0	69 3	69 4	69 8	69 8	70 2	70 6	71 0
170	69 3	69 7	69 7	70 1	70 1	70 5	70 6	71 0	71 3	71 7
171	70 1	70 5	70 5	71 0	71 0	71 4	71 4	71 8	72 1	72 6
172	71 0	71 5	71 4	71 9	71 9	72 3	72 3	72 7	73 1	73 5
173	71 9	72 4	72 3	72 8	72 8	73 2	73 2	73 7	74 0	74 4
174	72 3	73 3	73 2	73 6	73 7	74 1	74 2	74 6	74 8	75 2
175	73 7	74 1	74 1	74 5	74 6	75 1	75 1	75 5	75 7	76 1
176	74 6	75 0	75 0	75 5	75 5	76 0	76 0	76 4	76 6	77 0
177	75 5	75 9	75 9	76 3	76 4	76 9	76 9	77 3	77 5	77 9
178	76 4	76 9	76 8	77 3	77 3	77 9	77 8	78 3	78 4	78 9
179	77 5	78 1	77 9	78 5	78 4	78 9	78 8	79 4	79 4	79 9
180	78 6	79 1	79 0	79 5	79 4	80 0	79 9	80 5	80 4	80 9
181	79 7	80 2	80 1	80 6	80 5	81 0	81 0	81 5	81 4	81 9
182	80 7	81 3	81 2	81 7	81 5	82 1	82 0	82 6	82 4	83 1
183	81 8	82 4	82 2	82 8	82 6	83 1	83 1	83 7	83 6	84 3
184	82 9	83 4	83 3	83 9	83 7	84 3	84 2	84 8	84 8	85 5
185	84 0	84 5	84 4	84 9	84 8	85 4	85 3	85 9	86 0	86 6
186	85 1	85 7	85 6	86 2	86 0	86 6	86 4	87 0	87 3	87 9
187	86 4	87 0	86 8	87 5	87 2	87 9	87 7	88 3	88 6	89 2
188	87 6	88 2	88 1	88 7	88 5	89 1	88 9	89 5	89 8	90 4
189	88 8	89 4	89 3	90 0	89 7	90 4	90 2	90 8	91 1	91 7
190	90 1	90 7	90 6	91 2	91 0	91 6	91 5	92 1	92 4	93 0
191	91 3	91 9	91 8	92 4	92 2	92 8	92 8	93 4	93 6	94 2
192	92 6	93 1	93 1	93 6	93 4	94 0	94 0	94 7	94 9	95 6
193	93 4	94 0	94 3	94 7	94 8	95 4	95 2	95 8	96 1	96 6

TABLE

SWITCHMEN, U S A

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	5	10	20	30	40	50	60	70	80	90	95
							CENTILE					
						HEIGHT, cm						
40 44	281	164	167	170	172	174	175	177	178	180	184	186
45-49	243	165	168	170	172	173	175	176	178	179	182	184
50-54	152	164	166	168	170	172	174	175	177	179	181	184
55 59	159	164	165	167	169	171	172	174	176	178	180	183
						RELATIVE BODY WEIGHT Per Cent						
40 44	280	84	88	94	99	102	106	109	114	117	122	126
45 49	243	82	88	92	98	100	103	106	110	114	121	130
50-54	152	84	89	94	99	103	105	109	112	114	119	125
55-59	158	81	86	91	97	102	104	109	111	116	121	128
						SUM OF SKINFOLDS mm						
40-44	281	13	16	21	24	27	31	34	38	41	46	52
45-49	243	14	16	20	23	26	29	32	35	39	45	49
50-54	152	15	20	24	27	30	33	36	39	43	48	54
55-59	159	13	16	20	24	28	32	34	37	42	47	52
						SYSTOLIC BLOOD PRESSURE mm Hg						
40-44	281	110	114	120	124	127	130	134	140	145	157	164
45-49	243	110	113	120	125	129	133	137	143	151	165	171
50-54	153	112	118	123	130	131	136	140	148	158	170	185
55-59	159	116	120	126	130	135	140	149	156	165	175	188
						DIASTOLIC BLOOD PRESSURE 5th Phase, mm Hg						
40-44	281	70	71	76	79	60	83	86	88	91	99	102
45 49	243	70	74	77	80	80	84	88	90	95	101	108
50-54	153	71	74	76	80	81	85	89	90	96	105	110
55 59	159	70	73	78	80	83	88	90	93	100	107	112
						SERUM CHOLESTEROL CONCENTRATION mg per 100 ml						
40-44	278	170	183	201	213	225	233	245	256	274	291	320
45-49	239	174	181	199	213	222	232	244	259	274	295	324
50 54	150	192	194	206	218	224	232	244	256	274	294	319
55-59	156	167	190	208	224	236	250	262	273	283	297	319

TABLE

SEDENTARY CLERKS, U S A

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND 5, 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
		HEIGHT, cm										
40-44	166	165	166	169	173	173	175	176	178	180	182	185
45-49	185	163	166	169	170	172	174	175	177	180	182	184
50-54	239	162	164	167	169	170	172	173	176	177	181	183
55-59	267	162	164	167	169	170	172	173	175	177	180	183
		RELATIVE BODY WEIGHT, Per Cent										
40-44	166	82	87	91	94	100	103	107	110	113	119	124
45-49	185	82	87	92	97	99	102	104	106	111	116	122
50-54	238	82	87	93	96	99	102	106	110	114	122	125
55-59	267	82	86	90	95	98	101	104	107	111	120	124
		SUM OF SKINFOLDS, mm										
40-44	166	14	16	20	25	29	33	36	39	43	52	56
45-49	185	15	19	25	28	30	34	36	39	41	45	48
50-54	239	16	19	24	28	30	33	36	39	44	53	61
55-59	268	18	20	26	28	30	32	35	37	44	49	55
		SYSTOLIC BLOOD PRESSURE, mm Hg										
40-44	167	117	119	121	125	129	134	138	140	148	158	169
45-49	184	110	118	121	126	130	133	140	147	153	160	170
50-54	239	114	120	127	130	136	142	147	154	164	176	188
55-59	268	116	121	127	130	135	140	147	157	162	175	191
		DIASTOLIC BLOOD PRESSURE, 5th Phase, mm Hg										
40-44	167	66	70	76	79	80	83	87	90	94	100	108
45-49	184	70	72	76	80	81	85	88	90	95	100	108
50-54	239	70	74	80	82	85	88	90	93	98	102	11[illegible]
55-59	268	73	74	78	80	83	86	90	92	97	104	113
		SERUM CHOLESTEROL CONCENTRATION, mg per 100 ml										
40-44	163	167	182	195	207	220	234	245	259	280	300	317
45-49	185	170	183	196	207	220	234	245	258	280	301	326
50-54	238	175	187	206	215	224	232	243	256	269	283	318
55-59	267	178	190	207	217	229	242	253	267	280	297	312

TABLE

NON-SEDENTARY CLERKS, U S A

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5 10 20 ETC PER CENT OF THE MEN

AGE	NO MEN	5	10	20	30	40	50	60	70	80	90	95
HEIGHT cm												
40-44	32		167	169	171	172	173	175	176	180	181	
45-49	38		167	168	169	170	172	174	175	178	180	
50 54	38		164	165	169	171	172	174	176	178	182	
55-59	47		166	169	171	172	173	174	176	178	180	
RELATIVE BODY WEIGHT, Per Cent												
40 44	32		87	94	98	99	104	112	119	122	125	
45 49	38		86	89	93	97	100	106	109	112	115	
50 54	38		86	89	95	100	105	108	113	119	121	
55 59	47		85	91	95	97	101	105	109	115	126	
SUM OF SKINFOLDS, mm												
40 44	32		15	22	26	32	37	41	45	48	53	
45-49	39		12	16	23	30	34	35	38	43	48	
50 54	38		18	23	27	29	37	40	43	47	53	
55 59	47		21	24	27	29	31	33	35	41	51	
SYSTOLIC BLOOD PRESSURE mm Hg												
40-44	32		114	120	122	128	130	132	134	140	158	
45-49	39		114	120	127	129	133	137	142	149	153	
50 54	38		124	129	131	137	138	144	154	156	174	
55 59	47		120	128	134	141	144	156	163	172	194	
DIASTOLIC BLOOD PRESSURE 5th Phase mm Hg												
40 44	32		70	72	75	80	80	82	88	90	95	
45-49	39		69	72	77	78	80	82	86	89	95	
50-54	38		77	81	84	86	88	92	96	100	107	
55 59	47		72	78	82	84	90	92	96	99	111	
SERUM CHOLESTEROL CONCENTRATION mg per 100 ml												
40 44	31		182	193	211	224	228	232	248	268	290	
45 49	37		186	200	216	222	230	250	254	266	295	
50-54	38		204	214	235	246	255	271	281	308	328	
55-59	47		185	198	208	214	221	250	256	269	289	

TABLE

EXECUTIVES, U S A

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10, 20, ETC PER CENT OF THE MEN

AGE	NO. MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
							HEIGHT, cm					
40-44	46		170	172	174	176	177	180	181	182	188	
45-49	35		166	170	172	175	177	180	180	181	182	•
50-54	73	•	169	172	174	176	177	179	180	182	184	
55-59	96		168	170	172	174	176	178	179	182	183	•
							RELATIVE BODY WEIGHT, Per Cent					
40-44	46		87	95	97	102	106	108	110	112	116	•
45-49	35	•	89	93	95	100	103	106	108	112	116	•
50-54	73		92	96	100	102	103	107	110	113	115	•
55-59	96	•	88	90	95	99	101	105	108	111	119	
							SUM OF SKINFOLDS, mm					
40-44	46		18	22	26	29	33	36	40	43	52	
45-49	35		23	24	26	30	31	34	38	42	46	•
50-54	72		22	29	30	34	38	40	41	44	50	•
55-59	96	•	20	24	28	31	34	37	39	44	49	•
							SYSTOLIC BLOOD PRESSURE, mm Hg					
40-44	46		111	115	119	120	123	125	130	135	146	
45-49	35		114	118	120	124	130	130	138	145	153	
50-54	73		120	124	129	133	139	144	155	164	168	
55-59	97		120	124	128	130	133	137	146	154	168	
							DIASTOLIC BLOOD PRESSURE, 5th Phase, mm Hg					
40-44	46	•	71	74	76	78	80	82	85	91	95	
45-49	35	•	71	72	78	80	81	83	85	90	92	
50-54	73		78	80	82	86	89	90	95	98	103	
55-59	97		72	76	80	82	85	86	88	91	97	
							SERUM CHOLESTEROL CONCENTRATION, mg. per 100 ml					
40-44	45		179	198	204	222	242	251	258	268	274	
45-49	35	•	190	218	224	234	241	250	254	268	287	
50-54	72		194	206	216	230	243	255	262	298	320	•
55-59	95		197	208	219	234	247	254	260	274	288	

TABLE

CREVALCORE, ITALY

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
		HEIGHT cm										
40-44	174	158	161	163	166	167	169	171	173	174	176	179
45 49	303	156	160	162	165	167	168	169	170	172	175	178
50-54	291	158	160	162	165	166	168	170	171	173	176	177
55-59	219	155	158	161	163	165	167	168	170	173	175	178
		RELATIVE BODY WEIGHT, Per Cent										
40 44	175	85	88	92	96	101	105	110	114	120	128	133
45 49	300	82	86	91	96	100	103	107	111	116	124	128
50 54	288	84	87	91	96	99	102	105	110	114	122	128
55 59	216	84	86	90	94	98	101	104	112	118	125	132
		SUM OF SKINFOLDS mm										
40 44	176	10	12	14	17	21	23	26	29	32	40	43
45 49	303	10	11	14	17	18	21	26	30	34	38	42
50 54	294	10	12	15	18	20	22	25	28	32	37	42
55 59	218	9	12	14	17	20	22	25	30	36	41	46
		SYSTOLIC BLOOD PRESSURE mm Hg										
40 44	175	115	120	125	130	132	136	140	146	154	161	172
45 49	299	117	120	130	133	138	142	147	150	157	169	180
50 54	290	120	127	132	138	141	147	151	160	166	180	188
55-59	218	127	130	139	143	150	157	161	169	174	185	198
		DIASTOLIC BLOOD PRESSURE 5th Phase mm Hg										
40 44	175	70	73	76	79	80	84	88	90	92	98	107
45 49	299	71	75	78	80	84	87	90	91	95	100	109
50 54	289	73	77	80	81	85	88	90	92	97	104	10[illegible]
55 59	218	72	78	80	82	87	90	90	94	98	104	110
		SERUM CHOLESTEROL CONCENTRATION mg per 100 ml										
40-44	170	136	156	166	174	184	194	202	215	226	256	272
45 49	294	134	146	167	178	186	194	204	217	238	257	290
50 54	284	136	150	172	182	190	198	207	216	232	246	270
55-59	214	140	15[illegible]	170	179	190	204	216	226	241	257	267

TABLE

EXECUTIVES, U S A

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10, 20, ETC. PER CENT OF THE MEN

AGE	NO. MEN	CENTILE 5	10	20	30	40	50	60	70	80	90
						HEIGHT, cm					
40-44	46		170	172	174	176	177	180	181	182	188
45-49	35		166	170	172	175	177	180	180	181	182
50-54	73		169	172	174	176	177	179	180	182	184
55-59	96		168	170	172	174	176	178	179	182	183
						RELATIVE BODY WEIGHT, Per Cent					
40-44	46	•	87	95	97	102	106	108	110	112	116
45-49	35	•	89	93	95	100	103	106	108	112	116
50-54	73		92	96	100	102	103	107	110	113	115
55-59	96	•	88	90	95	99	101	105	108	111	119
						SUM OF SKINFOLDS, mm.					
40-44	46	•	18	22	26	29	33	36	40	43	52
45-49	35	•	23	24	26	30	31	34	38	42	46
50-54	72	•	22	29	30	34	38	40	41	44	50
55-59	96	•	20	24	28	31	34	37	39	44	49
						SYSTOLIC BLOOD PRESSURE, mm Hg					
40-44	46	•	111	115	119	120	123	125	130	135	146
45-49	35	•	114	118	120	124	130	130	138	145	153
50-54	73		120	124	129	133	139	144	155	164	168
55-59	97	•	120	124	128	130	133	137	146	154	168
						DIASTOLIC BLOOD PRESSURE, 5th Phase, mm Hg					
40-44	46	•	71	74	76	78	80	82	85	91	95
45-49	35	• •	71	72	78	80	81	83	85	90	92
50-54	73		78	80	82	86	89	90	95	98	103
55-59	97		72	76	80	82	85	86	88	91	97
						SERUM CHOLESTEROL CONCENTRATION, mg per 100 ml					
40-44	45	•	179	198	204	222	242	251	258	268	274
45-49	35	•	190	218	224	234	241	250	254	268	287
50-54	72		194	206	216	230	243	255	262	298	320
55-59	95	•	197	208	219	234	247	254	260	274	288

TABLE

CREVALCORE, ITALY

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND 5, 10 20, ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
						HEIGHT, cm						
40 44	174	158	161	163	166	167	169	171	173	174	176	179
45 49	303	156	160	162	165	167	168	169	170	172	175	178
50 54	291	158	160	162	165	166	168	170	171	173	176	177
55-59	219	155	158	161	163	165	167	168	170	173	175	178
						RELATIVE BODY WEIGHT, Per Cent						
40 44	175	85	88	92	96	101	105	110	114	120	128	133
45 49	300	82	86	91	96	100	103	107	111	116	124	128
50 54	288	84	87	91	96	99	102	105	110	114	122	128
55-59	216	84	86	90	94	98	101	104	112	118	125	132
						SUM OF SKINFOLDS mm						
40-44	176	10	12	14	17	21	23	26	29	32	40	43
45-49	303	10	11	14	17	18	21	26	30	34	38	42
50 54	294	10	12	15	18	20	22	25	28	32	37	42
55 59	218	9	12	14	17	20	22	25	30	36	41	46
						SYSTOLIC BLOOD PRESSURE mm Hg						
40-44	175	115	120	125	130	132	136	140	146	154	161	172
45-49	299	117	120	130	133	138	142	147	150	157	169	180
50 54	290	120	127	132	138	141	147	151	160	166	180	188
55-59	218	127	130	139	143	150	157	161	169	174	185	198
						DIASTOLIC BLOOD PRESSURE 5th Phase mm Hg						
40 44	175	70	73	76	79	80	84	88	90	92	98	107
45-49	299	71	75	78	80	84	87	90	91	95	100	109
50 54	283	73	77	80	81	85	88	90	92	97	104	10[illegible]
55-59	218	72	78	80	82	87	90	90	94	98	104	110
						SERUM CHOLESTEROL CONCENTRATION mg per 100 ml						
40 44	170	136	156	166	174	184	194	202	215	226	256	272
45 49	294	134	146	167	178	186	194	204	217	238	257	290
50 54	284	136	150	172	182	190	198	207	216	23[illegible]	246	270
55 59	214	140	152	170	179	190	204	216	226	241	257	287

TABLE

EXECUTIVES, U S A

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10, 20, ETC. PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90
						HEIGHT, cm					
40-44	46		170	172	174	176	177	180	181	182	188
45-49	35	•	166	170	172	175	177	180	180	181	182
50-54	73	•	169	172	174	176	177	179	180	182	184
55-59	96		168	170	172	174	176	178	179	182	183
						RELATIVE BODY WEIGHT, Per Cent					
40-44	46	•	87	95	97	102	106	108	110	112	116
45-49	35	•	89	93	95	100	103	106	108	112	116
50-54	73	•	92	96	100	102	103	107	110	113	115
55-59	96		88	90	95	99	101	105	108	111	119
						SUM OF SKINFOLDS, mm					
40-44	46		18	22	26	29	33	36	40	43	52
45-49	35		23	24	26	30	31	34	38	42	46
50-54	72		22	29	30	34	38	40	41	44	50
55-59	96	•	20	24	28	31	34	37	39	44	49
						SYSTOLIC BLOOD PRESSURE, mm Hg					
40-44	46		111	115	119	120	123	125	130	135	146
45-49	35		114	118	120	124	130	130	138	145	153
50-54	73		120	124	129	133	139	144	155	164	168
55-59	97		120	124	128	130	133	137	146	154	168
						DIASTOLIC BLOOD PRESSURE, 5th Phase, mm Hg					
40-44	46		71	74	76	78	80	82	85	91	95
45-49	35		71	72	78	80	81	83	85	90	92
50-54	73		78	80	82	86	89	90	95	98	103
55-59	97		72	76	80	82	85	86	88	91	97
						SERUM CHOLESTEROL CONCENTRATION, mg per 100 ml					
40-44	45		179	198	204	222	242	251	258	268	274
45-49	35		190	218	224	234	241	250	254	268	287
50-54	72		194	206	216	230	243	255	262	298	320
55-59	95	•	197	208	219	234	247	254	260	274	288

TABLE

CREVALCORE, ITALY

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10 20, ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
						HEIGHT, cm						
40 44	174	158	161	163	166	167	169	171	173	174	176	179
45 49	303	156	160	162	165	167	168	169	170	172	175	178
50 54	291	158	160	162	165	166	168	170	171	173	176	177
55-59	219	155	158	161	163	165	167	168	170	173	175	178
						RELATIVE BODY WEIGHT Per Cent						
40-44	175	85	88	92	96	101	105	110	114	120	128	133
45 49	300	82	86	91	96	100	103	107	111	116	124	128
50 54	288	84	87	91	96	99	102	105	110	114	122	128
55 59	216	84	86	90	94	98	101	104	112	118	125	132
						SUM OF SKINFOLDS mm						
40 44	176	10	12	14	17	21	23	26	29	32	40	43
45-49	303	10	11	14	17	18	21	26	30	34	38	42
50 54	294	10	12	15	18	20	22	25	28	32	37	42
55 59	218	9	12	14	17	20	22	25	30	36	41	46
						SYSTOLIC BLOOD PRESSURE, mm Hg						
40 44	175	115	120	125	130	132	136	140	146	154	161	172
45 49	299	117	120	130	133	138	142	147	150	157	169	180
50 54	290	120	127	132	138	141	147	151	160	166	180	188
55-59	218	127	130	139	143	150	157	161	169	174	185	198
						DIASTOLIC BLOOD PRESSURE 5th Phase mm Hg						
40 44	175	70	73	76	79	80	84	88	90	92	98	107
45-49	299	71	75	78	80	84	87	90	91	95	100	109
50 54	289	73	77	80	81	85	88	90	92	97	104	[illegible]
55-59	218	72	78	80	82	87	90	90	94	98	104	110
						SERUM CHOLESTEROL CONCENTRATION mg per 100 ml						
40 44	170	136	156	166	174	184	194	202	215	226	256	272
45-49	294	134	146	167	178	186	194	204	217	238	257	290
50 54	284	136	150	172	182	190	198	207	216	232	246	270
55-59	214	140	152	170	179	190	204	216	226	241	257	287

TABLE

MONTEGIORGIO, ITALY

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
						HEIGHT, cm						
40-44	123	157	159	162	163	164	165	167	168	170	174	177
45-49	246	156	157	160	162	164	165	166	168	169	172	174
50-54	217	154	156	158	160	162	163	164	167	169	171	173
55-59	130	154	156	158	160	161	162	164	166	168	171	173
						RELATIVE BODY WEIGHT, Per Cent						
40-44	123	80	82	89	92	96	99	102	107	110	117	123
45-49	246	80	84	88	92	95	98	102	108	112	120	128
50-54	217	77	81	84	89	92	94	99	103	107	114	122
55-59	130	78	79	82	86	88	94	97	102	108	121	125
						SUM OF SKINFOLDS, mm						
40-44	123	9	9	10	11	13	15	18	21	24	28	32
45-49	247	8	10	11	12	14	16	18	20	25	32	37
50-54	216	9	9	10	11	13	14	16	20	22	28	34
55-59	130	8	9	10	11	12	14	16	18	22	26	33
						SYSTOLIC BLOOD PRESSURE, mm Hg						
40-44	123	111	112	118	120	124	128	130	135	139	145	154
45-49	247	115	119	123	129	130	134	138	140	146	158	169
50-54	217	114	119	123	129	131	137	140	146	154	161	172
55-59	131	115	120	130	135	139	142	146	151	160	173	189
						DIASTOLIC BLOOD PRESSURE, 5th Phase, mm Hg						
40-44	123	68	70	70	72	76	78	80	80	82	91	95
45-49	247	70	70	74	76	79	80	82	84	90	93	98
50-54	217	70	70	75	78	80	81	83	89	90	98	102
55-59	131	70	72	76	80	81	83	85	88	90	97	108
						SERUM CHOLESTEROL CONCENTRATION mg per 100 ml						
40-44	122	150	157	165	175	184	192	201	210	224	249	264
45-49	244	144	155	169	183	192	200	208	219	235	257	290
50-54	216	148	157	169	182	191	199	207	222	232	248	268
55-59	128	155	162	173	183	191	198	203	213	228	263	273

TABLE

NICOTERA ITALY

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5 10 20 ETC PER CENT OF THE MEN

AGE	NO MEN	5	10	20	30	40	50	60	70	80	90	95
							HEIGHT cm					
45 49	230		154	158	160	161	163	165	167	169	172	
50 54	173		155	157	158	162	163	165	166	169	173	
55 59	117		155	157	159	160	162	164	166	168	170	
							RELATIVE BODY WEIGHT Per Cent					
45 49	230		78	82	86	87	94	99	104	111	118	
50 54	123		74	78	81	85	87	92	98	102	114	
55 59	117		76	78	83	87	91	97	102	106	116	
							SUM OF SKINFOLDS mm					
45 49	230		9	10	11	12	13	16	19	26	32	
50 54	123		8	9	10	11	13	15	17	19	25	
55 59	117		8	10	12	13	14	16	19	22	27	
							SYSTOLIC BLOOD PRESSURE mm Hg					
45 49	230		110	114	118	122	125	128	132	138	142	
50 54	123		111	116	118	122	127	132	136	142	158	
55 59	117		113	120	126	130	136	140	145	150	170	
							DIASTOLIC BLOOD PRESSURE 5th Phase mm Hg					
45 49	230		64	68	70	72	75	77	80	80	84	
50 54	123		64	70	70	72	75	78	80	83	88	
55 59	117		64	70	72	75	78	80	82	85	90	
							SERUM CHOLESTEROL CONCENTRATION mg per 100 ml					
45 49	31			144			184			227		
50 54	19			137			174			192		
55 59	18			152			166			217		

TABLE

MONTEGIORGIO, ITALY

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	5	10	20	30	40	50	60	70	80	90	95
						CENTILE						
						HEIGHT, cm						
40-44	123	157	159	162	163	164	165	167	168	170	174	177
45-49	246	156	157	160	162	164	165	166	168	169	172	174
50-54	217	154	156	158	160	162	163	164	167	169	171	173
55-59	130	154	156	158	160	161	162	164	166	168	171	173
						RELATIVE BODY WEIGHT, Per Cent						
40-44	123	80	82	89	92	96	99	102	107	110	117	123
45-49	246	80	84	88	92	95	98	102	108	112	120	128
50-54	217	77	81	84	89	92	94	99	103	107	114	122
55-59	130	78	79	82	86	88	94	97	102	108	121	125
						SUM OF SKINFOLDS, mm						
40-44	123	9	9	10	11	13	15	18	21	24	28	32
45-49	247	8	10	11	12	14	16	18	20	25	32	37
50-54	216	9	9	10	11	13	14	16	20	22	28	34
55-59	130	8	9	10	11	12	14	16	18	22	26	33
						SYSTOLIC BLOOD PRESSURE mm Hg						
40-44	123	111	112	118	120	124	128	130	135	139	145	154
45-49	247	115	119	123	129	130	134	138	140	146	158	169
50-54	217	114	119	123	129	131	137	140	146	154	161	172
55-59	131	115	120	130	135	139	142	146	151	160	173	189
						DIASTOLIC BLOOD PRESSURE, 5th Phase, mm Hg						
40-44	123	68	70	70	72	76	78	80	80	82	91	95
45-49	247	70	70	74	76	79	80	82	84	90	93	98
50-54	217	70	70	75	78	80	81	83	89	90	98	102
55-59	131	70	72	76	80	81	83	85	88	90	97	108
						SERUM CHOLESTEROL CONCENTRATION, mg per 100 ml						
40-44	122	150	157	165	175	184	192	201	210	224	249	264
45-49	244	144	155	169	183	192	200	208	219	235	257	290
50-54	216	148	157	169	182	191	199	207	222	232	248	268
55-59	128	155	162	173	183	191	198	203	213	228	263	273

TABLE

SLAVONIA YUGOSLAVIA

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5 10, 20 ETC PER CENT OF THE MEN

AGE	NO MEN	5	10	20	30	40	50	60	70	80	90	95
		CENTILE										
HEIGHT, cm												
40-44	102	160	161	164	166	168	170	172	173	175	178	181
45-49	182	160	162	163	165	166	168	169	170	173	175	177
50-54	197	155	159	161	163	165	166	168	170	172	175	179
55-59	216	158	161	163	165	166	168	169	171	173	176	179
RELATIVE BODY WEIGHT Per Cent												
40-44	102	78	81	85	88	93	95	100	103	106	112	123
45-49	181	78	80	84	88	91	94	97	103	107	120	127
50 54	197	75	77	81	83	86	88	92	98	103	114	121
55 59	215	74	77	80	84	88	91	93	98	104	111	116
SUM OF SKINFOLDS mm												
40-44	102	9	10	10	12	13	15	18	20	23	28	37
45-49	181	8	9	10	11	13	15	17	22	26	33	42
50-54	197	8	9	10	10	12	13	14	16	22	31	40
55-59	215	8	9	10	11	12	14	15	17	22	27	35
SYSTOLIC BLOOD PRESSURE mm Hg												
40-44	102	108	111	120	125	130	130	135	140	146	165	171
45-49	180	112	116	120	125	130	130	137	140	151	163	170
50 54	197	110	115	120	128	130	131	139	144	152	161	172
55-59	216	110	115	123	130	138	140	146	152	162	171	180
DIASTOLIC BLOOD PRESSURE, 5th Phase mm Hg												
40 44	102	66	68	70	75	78	79	80	85	90	97	105
45-49	180	68	69	72	77	78	80	85	89	90	100	108
50 54	197	66	68	70	76	78	80	82	86	89	96	106
55-59	216	64	68	72	78	80	84	86	90	95	100	104
SERUM CHOLESTEROL CONCENTRATION mg per 100 ml.												
40 44	95	141	149	162	178	186	196	210	217	232	249	273
45-49	176	140	147	159	177	186	197	207	218	237	255	275
50-54	192	140	152	164	176	186	200	206	217	232	260	270
55 59	213	136	146	162	174	182	194	202	220	234	256	275

TABLE

DALMATIA, YUGOSLAVIA

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
		HEIGHT, cm										
40-44	85	165	166	169	171	173	175	176	178	179	182	186
45-49	183	162	166	168	170	171	173	174	176	178	182	184
50-54	211	163	165	169	170	172	173	175	177	179	182	184
55-59	190	161	165	166	169	170	172	174	175	177	180	184
		RELATIVE BODY WEIGHT, *Per Cent*										
40-44	86	78	82	84	86	90	94	98	102	103	108	115
45-49	184	78	80	85	88	90	93	95	98	104	111	116
50-54	212	76	78	83	85	87	90	92	96	100	107	113
55-59	189	74	77	79	82	85	88	91	97	103	111	117
		SUM OF SKINFOLDS, mm										
40-44	85	9	10	11	12	13	15	17	21	24	34	37
45-49	184	9	10	10	12	13	15	17	20	25	31	36
50-54	212	8	9	10	11	12	14	16	18	23	28	31
55-59	189	8	9	10	10	11	13	15	17	24	32	36
		SYSTOLIC BLOOD PRESSURE mm Hg										
40-44	84	110	115	126	130	131	136	140	141	147	160	169
45-49	184	110	120	121	125	130	135	138	140	150	164	170
50-54	212	115	120	122	130	131	137	140	145	155	165	175
55-59	192	112	120	124	130	130	135	140	150	152	165	175
		DIASTOLIC BLOOD PRESSURE, 5th Phase mm Hg										
40-44	84	66	70	70	76	80	85	89	90	92	95	102
45-49	184	68	70	70	75	79	80	82	88	92	96	102
50-54	212	68	70	70	75	79	82	85	90	92	98	100
55-59	192	68	70	74	77	80	82	85	88	92	99	102
		SERUM CHOLESTEROL CONCENTRATION mg per 100 ml										
40-44	84	136	146	155	163	176	182	200	214	227	251	270
45-49	181	119	141	156	168	176	185	198	208	220	237	246
50-54	211	126	136	155	166	174	186	198	208	225	241	260
55-59	190	130	142	152	164	177	188	198	208	222	246	260

TABLE

WEST FINLAND

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5 10 20 ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
		HEIGHT, cm										
40-44	166	162	164	168	169	171	173	174	175	177	180	182
45-49	221	162	164	167	168	170	171	173	174	176	178	181
50-54	240	161	163	167	168	170	172	173	174	176	178	181
55-59	220	160	162	165	167	169	170	171	173	175	178	178
		RELATIVE BODY WEIGHT Per Cent										
40-44	164	82	86	90	93	95	98	101	104	107	115	124
45-49	216	80	82	86	90	94	96	100	105	109	115	122
50-54	238	80	82	85	89	92	97	101	104	109	115	130
55-59	217	77	80	85	88	92	95	98	101	105	114	119
		SUM OF SKINFOLDS, mm										
40-44	168	10	11	12	13	15	16	19	21	25	32	39
45-49	224	10	11	12	13	15	16	19	21	26	32	40
50-54	245	9	11	12	13	15	16	19	23	27	35	40
55-59	222	9	10	11	12	14	16	19	21	24	31	40
		SYSTOLIC BLOOD PRESSURE mm Hg										
40 44	168	109	112	120	125	130	133	136	141	147	159	169
45-49	224	114	119	122	126	130	135	139	142	148	156	162
50-54	245	113	118	124	130	134	139	143	146	152	165	178
55-59	222	115	121	129	132	139	143	150	155	164	177	186
		DIASTOLIC BLOOD PRESSURE 5th Phase mm Hg										
40-44	168	65	67	70	74	78	80	80	83	86	92	98
45-49	224	68	70	74	77	78	80	81	85	88	92	96
50-54	245	68	70	73	78	80	82	84	88	90	100	104
55-59	222	70	72	76	78	80	82	86	89	90	97	101
		SERUM CHOLESTEROL CONCENTRATION mg per 100 ml										
40-44	168	193	201	216	227	238	248	260	278	293	314	335
45-49	223	186	201	216	228	242	255	267	277	300	319	346
50-54	244	178	197	214	231	245	257	277	284	306	323	348
55 59	222	182	195	216	228	238	251	258	269	282	305	325

TABLE

KARELIA, FINLAND

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND 5, 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
						HEIGHT, cm						
40-44	207	160	161	164	165	167	168	170	172	174	177	179
45-49	234	158	161	163	165	166	168	169	171	173	177	178
50-54	196	158	160	163	165	167	168	170	171	172	174	176
55-59	168	158	159	162	163	165	167	169	170	172	175	177
						RELATIVE BODY WEIGHT, Per Cent						
40-44	205	80	83	86	90	92	94	97	101	104	110	116
45-49	230	79	82	86	89	92	94	98	102	106	110	118
50-54	191	76	79	83	86	89	93	95	99	105	111	117
55-59	168	76	78	82	85	89	90	93	96	101	110	119
						SUM OF SKINFOLDS, mm						
40-44	207	9	10	11	12	13	13	15	18	22	28	35
45-49	239	9	10	11	12	13	15	18	20	25	31	35
50-54	197	9	9	11	11	13	14	17	21	24	30	36
55-59	172	8	8	10	11	12	14	16	18	22	32	40
						SYSTOLIC BLOOD PRESSURE, mm Hg						
40-44	206	120	124	130	135	138	141	145	150	154	164	168
45-49	235	120	125	130	134	138	140	145	150	160	173	185
50-54	197	121	130	135	139	143	149	154	158	169	179	188
55-59	171	127	130	139	144	148	153	160	166	174	184	208
						DIASTOLIC BLOOD PRESSURE, 5th Phase, mm Hg						
40-44	206	70	75	80	80	85	87	90	90	95	100	102
45-49	235	74	78	80	82	85	88	90	92	98	102	110
50-54	197	70	77	80	85	88	90	92	96	100	104	110
55-59	170	72	78	81	86	90	90	94	98	100	107	110
						SERUM CHOLESTEROL CONCENTRATION, mg per 100 ml						
40-44	207	181	193	220	232	248	265	276	288	302	328	360
45-49	239	197	208	222	239	259	272	284	295	313	335	360
50-54	196	191	208	220	238	251	262	280	302	315	340	358
55-59	172	162	190	211	231	245	259	268	280	292	317	343

TABLE

CRETE GREECE

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10 20, ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
						HEIGHT, cm						
40 44	158	157	159	162	163	165	166	168	170	172	174	178
45 49	199	156	158	161	163	165	166	168	169	171	174	176
50 54	172	157	159	161	164	165	166	168	170	171	174	176
55 59	146	156	158	160	162	164	165	167	168	170	173	174
						RELATIVE BODY WEIGHT Per Cent						
40 44	157	80	82	86	88	92	94	96	100	104	112	117
45 49	200	76	79	82	85	88	91	94	97	103	111	116
50 54	172	73	75	81	84	88	92	94	98	102	112	117
55 59	146	75	77	81	84	86	88	90	94	97	103	104
						SUM OF SKINFOLDS mm						
40 44	160	9	10	10	12	13	14	17	20	24	30	36
45 49	202	9	10	10	11	12	14	15	18	22	28	33
50 54	175	8	9	10	12	13	15	17	20	23	27	32
55 59	148	9	10	10	11	13	14	15	17	19	23	27
						SYSTOLIC BLOOD PRESSURE mm Hg						
40 44	158	110	112	118	122	128	131	136	142	150	155	165
45-49	201	110	116	120	123	130	132	136	140	145	155	166
50 54	173	110	115	122	127	130	135	139	145	152	164	175
55 59	146	113	119	125	130	134	138	145	152	160	174	188
						DIASTOLIC BLOOD PRESSURE 5th Phase mm Hg						
40 44	158	62	68	72	75	76	80	82	87	90	96	100
45 49	201	65	70	72	75	78	80	82	85	89	97	99
50 54	173	63	70	72	75	80	81	85	89	90	95	101
55-59	146	69	70	73	75	80	83	85	89	90	94	100
						SERUM CHOLESTEROL CONCENTRATION mg per 100 ml						
40 44	152	148	156	169	177	186	198	206	217	233	260	270
45-49	190	143	154	169	178	188	199	206	219	235	251	272
50 54	167	153	158	176	183	195	210	218	232	250	270	282
55 59	143	155	163	172	193	199	208	226	235	245	257	284

TABLE

ZUTPHEN, NETHERLANDS

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
						HEIGHT, cm						
40-44	181	164	165	168	171	174	175	177	179	180	183	185
45-49	237	164	166	169	172	174	175	176	178	180	183	184
50-54	235	163	166	168	170	172	174	175	177	180	182	185
55-59	225	162	163	167	169	171	172	174	176	178	182	184
						RELATIVE BODY WEIGHT, Per Cent						
40-44	181	82	85	91	93	96	99	102	105	108	111	115
45-49	236	83	85	89	92	95	97	100	103	106	111	118
50-54	234	79	82	88	91	95	97	100	102	105	113	115
55-59	224	79	82	87	91	94	97	99	101	106	110	114
						SUM OF SKINFOLDS, mm						
40-44	181	12	14	16	20	22	24	27	29	32	38	40
45-49	236	11	13	16	20	22	23	26	28	32	37	40
50-54	234	12	13	16	20	22	24	26	30	32	37	44
55-59	225	12	14	16	18	21	22	26	28	32	38	40
						SYSTOLIC BLOOD PRESSURE, mm Hg.						
40-44	181	120	125	130	130	136	140	145	150	153	160	170
45-49	236	117	120	129	130	135	140	145	150	156	165	178
50-54	233	118	120	128	132	138	140	146	155	163	175	180
55-59	225	120	122	130	135	140	145	150	158	168	176	188
						DIASTOLIC BLOOD PRESSURE, 5th Phase, mm Hg						
40-44	180	70	75	80	80	85	90	90	94	98	100	106
45-49	236	70	73	80	80	85	90	90	93	98	104	110
50-54	233	72	75	80	80	85	90	90	95	100	108	118
55-59	225	70	75	80	82	85	88	90	95	100	106	110
						SERUM CHOLESTEROL CONCENTRATION, mg per 100 ml						
40-44	174	168	177	198	209	224	233	244	253	268	285	306
45-49	219	170	186	201	215	226	235	247	257	272	298	320
50-54	224	176	187	200	209	219	227	239	252	265	289	315
55-59	214	164	177	197	206	217	226	238	252	264	292	324

TABLE

TANUSHIMARU JAPAN

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	5	10	20	30	40	50	60	70	80	90	95
							CENTILE					
						HEIGHT, cm						
40 44	112	152	155	157	159	160	162	163	164	165	167	169
45-49	117	151	154	156	158	160	161	162	164	165	168	170
50 54	137	151	153	155	157	158	159	161	163	165	167	170
55-59	143	151	152	154	156	159	160	161	162	163	165	167
						RELATIVE BODY WEIGHT, Per Cent						
40-44	111	76	80	82	85	87	89	91	94	95	98	102
45-49	116	72	77	79	82	84	86	88	90	93	100	104
50 54	137	71	75	79	80	82	84	87	90	93	100	109
55-59	143	73	75	79	81	82	84	86	89	92	99	102
						SUM OF SKINFOLDS, mm						
40-44	110	10	11	12	12	14	15	16	18	22	23	24
45 49	113	10	10	12	13	14	15	17	18	21	24	28
50 54	136	9	10	11	12	14	14	16	17	21	26	32
55-59	140	10	11	12	12	13	15	16	18	21	26	28
						SYSTOLIC BLOOD PRESSURE mm Hg						
40-44	112	96	102	110	112	117	120	124	132	138	145	154
45-49	117	103	108	114	118	120	128	132	136	142	152	164
50-54	137	105	110	114	120	125	132	137	140	146	160	173
55 59	143	107	112	120	124	132	138	148	156	166	183	209
						DIASTOLIC BLOOD PRESSURE 5th Phase mm Hg						
40 44	112	50	51	58	62	64	68	70	74	78	83	86
45-49	117	51	58	62	68	70	70	74	78	84	90	93
50 54	137	56	60	64	68	70	72	75	80	82	90	105
55 59	143	58	60	64	70	71	78	80	88	92	100	105
						SERUM CHOLESTEROL CONCENTRATION mg per 100 ml						
40 44	109	97	109	140	147	157	167	183	212	237	277	298
45-49	111	107	111	131	147	155	165	185	198	220	259	311
50-54	132	106	114	133	149	164	178	187	216	231	266	290
55-59	139	109	116	134	144	155	168	183	205	225	257	313

TABLE

CORFU, GREECE

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10, 20, ETC PER CENT OF THE MEN

AGE	NO. MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	
						HEIGHT, cm						
40-44	120	157	159	162	164	166	167	169	172	174	176	17
45-49	114	154	158	161	162	164	166	167	170	172	177	17
50-54	169	156	159	160	162	164	166	167	169	170	172	17
55-59	126	155	158	160	161	162	164	165	166	168	172	17
						RELATIVE BODY WEIGHT, Per Cent						
40-44	120	78	80	84	88	92	94	100	102	106	114	12
45-49	114	76	79	83	87	89	93	100	104	110	115	11
50-54	168	75	77	82	85	88	92	95	98	103	110	12
55-59	126	74	77	80	83	87	90	94	97	103	111	12
						SUM OF SKINFOLDS, mm						
40-44	120	9	10	11	12	14	16	19	20	24	30	3
45-49	114	9	10	11	12	14	15	18	20	26	31	3
50-54	169	9	10	11	12	13	14	16	19	23	31	4
55-59	126	9	10	10	11	12	14	16	19	24	30	3
						SYSTOLIC BLOOD PRESSURE, mm Hg						
40-44	120	105	109	115	121	128	130	134	138	140	154	164
45-49	114	102	110	119	121	125	130	134	139	146	160	173
50-54	169	110	111	120	125	130	134	138	140	151	164	176
55-59	126	110	111	120	125	130	135	140	150	158	167	175
						DIASTOLIC BLOOD PRESSURE, 5th Phase, mm Hg						
40-44	120	65	70	72	76	80	81	82	85	89	92	100
45-49	114	67	70	72	75	79	80	82	86	90	98	107
50-54	169	70	71	75	78	80	81	85	89	90	97	108
55-59	126	65	70	74	76	80	81	85	86	90	95	100
						SERUM CHOLESTEROL CONCENTRATION, mg per 100 ml						
40-44	120	139	146	158	172	185	193	203	220	232	262	309
45-49	111	140	147	163	176	193	203	209	222	233	259	300
50-54	165	141	162	174	186	194	202	216	232	246	258	274
55-59	125	142	154	171	180	186	194	201	212	227	251	264

TABLE

TANUSHIMARU, JAPAN

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	5	10	20	30	40	50	60	70	80	90	95
						CENTILE						
						HEIGHT, cm						
40-44	112	152	155	157	159	160	162	163	164	165	167	169
45 49	117	151	154	156	158	160	161	162	164	165	168	170
50 54	137	151	153	155	157	158	159	161	163	165	167	170
55 59	143	151	152	154	156	159	160	161	162	163	165	167
						RELATIVE BODY WEIGHT, Per Cent						
40 44	111	76	80	82	85	87	89	91	94	95	98	102
45-49	116	72	77	79	82	84	86	88	90	93	100	104
50 54	137	71	75	79	80	82	84	87	90	93	100	109
55 59	143	73	75	79	81	82	84	86	89	92	99	102
						SUM OF SKINFOLDS mm						
40-44	110	10	11	12	12	14	15	16	18	22	23	24
45 49	113	10	10	12	13	14	15	17	18	21	24	28
50-54	136	9	10	11	12	14	14	16	17	21	26	32
55 59	140	10	11	12	12	13	15	16	18	21	26	28
						SYSTOLIC BLOOD PRESSURE mm Hg						
40-44	112	96	102	110	112	117	120	124	132	138	145	154
45 49	117	103	108	114	118	120	128	132	136	142	152	164
50 54	137	105	110	114	120	125	132	137	140	146	160	173
55 59	143	107	112	120	124	132	138	148	156	166	183	209
						DIASTOLIC BLOOD PRESSURE 5th Phase mm Hg						
40 44	112	50	51	58	62	64	68	70	74	78	83	86
45 49	117	51	58	62	68	70	70	74	78	84	90	93
50 54	137	56	60	64	68	70	72	75	80	82	90	105
55 59	143	58	60	64	70	71	78	80	88	92	100	105
						SERUM CHOLESTEROL CONCENTRATION mg per 100 ml						
40 44	109	97	109	140	147	157	167	183	212	237	277	298
45 49	111	107	111	131	147	155	165	185	198	220	259	311
50 54	132	106	114	133	149	164	178	187	216	231	266	290
55-59	139	109	116	134	144	155	168	183	205	225	257	313

TABLE

USHIBUKA, JAPAN

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
						HEIGHT, cm						
40-44	107	152	153	156	157	159	160	161	162	165	167	170
45-49	114	152	153	156	157	159	160	162	163	165	167	169
50-54	129	149	151	154	156	157	158	160	161	163	165	168
55-59	107	148	150	153	156	157	159	160	162	165	168	169
						RELATIVE BODY WEIGHT, Per Cent						
40-44	107	74	77	82	85	88	91	93	96	99	102	107
45-49	114	76	78	81	84	87	89	91	93	96	101	109
50-54	129	76	77	80	82	85	87	88	90	92	97	103
55-59	107	68	72	77	80	82	84	86	88	92	96	101
						SUM OF SKINFOLDS, mm						
40-44												
45-49												
50-54						Data Not Available						
55-59												
						SYSTOLIC BLOOD PRESSURE, mm Hg						
40-44	115	105	110	114	120	120	126	132	135	140	152	169
45-49	128	102	107	114	120	120	128	135	145	155	165	174
50-54	139	110	112	118	125	130	135	140	150	156	176	195
55-59	118	110	114	120	128	135	140	144	154	165	181	213
						DIASTOLIC BLOOD PRESSURE, 5th Phase, mm Hg						
40-44	115	52	60	66	70	72	75	78	80	82	90	95
45-49	128	60	64	68	70	74	76	80	80	90	97	100
50-54	139	60	65	70	72	75	80	80	84	87	96	104
55-59	118	64	67	70	74	77	80	84	86	90	96	105
						SERUM CHOLESTEROL CONCENTRATION, mg per 100 ml						
40-44	112	100	106	114	122	130	142	150	155	164	181	195
45-49	127	103	109	114	124	133	143	153	158	169	182	195
50-54	136	89	103	114	122	132	137	146	158	168	179	189
55-59	118	94	107	116	126	134	144	152	161	171	184	196

TABLE

RAILWAYMEN, ROME, ITALY

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, *10, 20,* ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
						HEIGHT, cm						
40-44	197	158	160	162	163	165	166	167	169	172	175	176
45-49	215	156	159	162	164	165	166	168	169	170	172	174
50 54	231	156	158	161	163	164	165	166	168	170	172	174
55-59	124	156	157	159	161	163	164	166	168	170	173	176
						RELATIVE BODY WEIGHT, Per Cent						
40-44	197	86	90	95	100	104	108	113	117	121	127	131
45-49	215	86	90	96	100	104	108	112	116	122	129	136
50 54	231	83	87	95	99	103	106	110	113	118	125	128
55-59	124	78	82	93	100	104	108	112	114	121	126	129
						SUM OF SKINFOLDS mm						
40-44	197	13	14	17	20	22	26	30	34	38	44	49
45-49	215	12	15	19	21	23	27	30	33	38	45	50
50 54	231	11	13	16	20	23	25	28	32	36	40	45
55-59	124	10	13	17	20	23	26	29	30	34	39	43
						SYSTOLIC BLOOD PRESSURE, mm Hg						
40 44	197	113	119	123	129	131	135	138	140	147	158	168
45-49	215	116	118	128	133	136	138	141	145	151	160	169
50-54	232	115	118	126	130	135	138	141	148	152	162	173
55-59	124	119	122	129	135	140	142	150	155	166	174	184
						DIASTOLIC BLOOD PRESSURE, 5th Phase mm Hg						
40-44	197	68	70	76	80	83	86	89	91	96	102	108
45-49	215	70	72	79	80	84	89	90	95	100	106	110
50 54	232	70	72	80	82	86	89	90	93	98	105	110
55 59	124	73	78	80	85	88	90	91	97	100	103	107
						SERUM CHOLESTEROL CONCENTRATION mg per 100 ml						
40-44	195	146	154	168	182	196	207	216	225	234	252	262
45-49	214	147	159	173	185	197	206	218	229	240	260	284
50-54	231	147	159	173	186	198	209	219	231	242	267	283
55-59	124	153	158	170	183	193	204	212	225	239	261	270

TABLE

USHIBUKA, JAPAN

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10, 20, ETC PER CENT OF THE MEN

AGE	NO MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
						HEIGHT, cm						
40-44	107	152	153	156	157	159	160	161	162	165	167	170
45-49	114	152	153	156	157	159	160	162	163	165	167	169
50-54	129	149	151	154	156	157	158	160	161	163	165	168
55-59	107	148	150	153	156	157	159	160	162	165	168	169
					RELATIVE BODY WEIGHT, Per Cent							
40-44	107	74	77	82	85	88	91	93	96	99	102	107
45-49	114	76	78	81	84	87	89	91	93	96	101	109
50-54	129	76	77	80	82	85	87	88	90	92	97	103
55-59	107	68	72	77	80	82	84	86	88	92	96	101
						SUM OF SKINFOLDS, mm						
40-44												
45-49												
50-54						Data Not Available						
55-59												
				SYSTOLIC BLOOD PRESSURE, mm, Hg								
40-44	115	105	110	114	120	120	126	132	135	140	152	169
45-49	128	102	107	114	120	120	128	135	145	155	165	174
50-54	139	110	112	118	125	130	135	140	150	156	176	195
55-59	118	110	114	120	128	135	140	144	154	165	181	213
				DIASTOLIC BLOOD PRESSURE, 5th Phase, mm Hg.								
40-44	115	52	60	66	70	72	75	78	80	82	90	95
45-49	128	60	64	68	70	74	76	80	80	90	97	100
50-54	139	60	65	70	72	75	80	80	84	87	96	104
55-59	118	61	67	70	74	77	80	84	86	90	96	105
			SERUM CHOLESTEROL CONCENTRATION, mg per 100 ml									
40-44	112	100	106	114	122	130	142	150	155	164	181	195
45-49	127	103	109	114	124	133	143	153	158	169	182	195
50-54	136	89	103	114	122	132	137	146	158	168	179	189
55-59	118	94	107	116	126	134	144	152	161	171	184	196

TABLE

D stributions of thickness of the skinfold over the triceps muscle Entries in the table are the cutting points, in mm , for the centiles given in the column headings. Below these values 5, 10, 20 etc , per cent of the men are found

AGE	NO MEN	5	10	20	30	40	50	60	70	80	90	95
						CENTILES						
U S A RAILROAD SWITCHMEN												
40 44	282	6	6	8	10	10	12	14	15	17	19	21
45-49	241	6	6	8	9	10	11	12	14	15	18	20
50 54	153	6	8	9	10	12	12	14	15	16	19	22
55 59	159	5	6	8	10	10	12	14	15	16	19	22
U S A RAILROAD SEDENTARY CLERKS												
40-44	166	6	6	8	10	12	13	14	16	18	21	24
45 49	185	6	7	10	11	12	13	15	16	17	20	21
50 54	239	6	8	9	10	12	13	14	16	18	20	24
55-59	269	6	8	10	10	12	12	14	16	18	21	22
U S A RAILROAD NON SEDENTARY CLERKS												
40 44	31	-	6	10	12	13	16	18	18	20	22	--
45-49	39	-	6	7	9	10	12	15	16	18	20	--
50 54	38	-	8	9	10	12	13	16	18	18	25	--
55 59	47		10	10	12	12	14	14	16	17	20	--
U S A RAILROAD EXECUTIVES												
40 44	46	-	8	10	12	13	14	16	18	19	20	--
45 49	35		8	10	11	12	12	14	16	18	20	--
50 54	73		8	10	12	12	14	15	18	18	22	--
55 59	96		8	9	12	12	14	15	16	18	20	--
NICOTERA ITALY												
40 44	0		--	-	-		-	-	-	-		--
45 49	229	3	4	4	4	4	5	6	8	10	13	15
50 54	123	3	3	4	4	4	5	6	6	8	9	12
55 59	117	3	3	4	4	5	5	6	7	8	10	12

TABLE

VELIKA KRSNA (SERBIA) YUGOSLAVIA

CENTILES (CUTTING POINTS) BELOW WHICH ARE FOUND

5, 10, 20, ETC PER CENT OF THE MEN

AGE	NO. MEN	CENTILE 5	10	20	30	40	50	60	70	80	90	95
		HEIGHT, cm										
40-44	136	160	163	164	167	169	171	172	173	175	178	180
45-49	81	161	163	164	166	168	170	171	173	174	178	180
50-54	135	157	160	163	165	167	168	170	172	174	176	178
55-59	158	159	161	164	166	167	168	170	172	174	177	179
		RELATIVE BODY WEIGHT, Per Cent										
40-44	136	80	81	85	86	88	89	92	95	99	109	114
45-49	81	66	78	81	84	87	88	91	94	100	109	115
50-54	135	76	78	81	83	85	88	90	93	96	103	109
55-59	158	73	76	78	80	83	86	89	92	95	101	108
		SUM OF SKINFOLDS, mm										
40-44	136	9	10	10	11	12	13	14	16	18	23	27
45-49	81	9	9	10	11	12	13	14	15	18	25	31
50-54	135	9	9	10	11	12	13	14	15	18	22	28
55-59	158	8	9	10	11	11	12	14	15	19	24	27
		SYSTOLIC BLOOD PRESSURE, mm Hg										
40-44	136	106	109	112	120	120	124	127	130	130	141	148
45-49	82	107	110	117	120	121	128	130	132	140	148	156
50-54	135	110	110	119	124	128	130	133	139	144	157	170
55-59	158	110	115	120	128	130	130	140	143	150	160	177
		DIASTOLIC BLOOD PRESSURE, 5th Phase mm Hg										
40-44	136	67	69	70	76	77	78	80	81	87	90	98
45-49	81	70	70	76	77	78	80	81	84	88	93	97
50-54	135	70	70	76	78	80	80	84	86	88	96	100
55-59	158	69	70	76	79	80	80	85	88	90	98	105
		SERUM CHOLESTEROL CONCENTRATION, mg per 100 ml										
40-44	136	112	121	133	141	149	154	162	168	179	191	203
45-49	82	115	120	132	143	151	157	168	178	194	201	226
50-54	135	111	116	133	144	152	159	168	179	186	204	216
55-59	158	119	126	134	139	149	155	164	179	190	207	219

TABLE

Triceps skinfold thickness

AGE	NO MEN	CENTILES 5	10	20	30	40	50	60	70	80	90	95
ZUTPHEN NETHERLANDS												
40 44	181	4	6	6	8	8	10	10	12	14	16	18
45 49	237	4	5	6	8	8	9	10	11	12	14	16
50 54	234	4	5	6	8	8	10	10	12	13	15	18
55 59	225	4	6	6	7	8	10	10	11	12	14	16
CRETE GREECE												
40-44	160	3	4	4	4	5	6	6	8	10	13	14
45 49	202	3	4	4	4	5	5	7	8	10	14	20
50-54	175	3	3	4	5	5	6	7	8	10	11	12
55 59	148	3	3	4	4	5	5	6	6	7	9	11
CORFU GREECE												
40 44	120	4	4	4	5	5	6	7	9	10	11	15
45 49	114	3	4	4	4	5	6	7	8	10	12	15
50 54	169	4	4	4	4	5	6	6	8	9	12	16
55-59	126	3	4	4	4	4	5	6	7	10	12	15
ROME ITALY RAILROAD EMPLOYEES												
40 44	196	5	6	7	8	9	10	11	12	14	17	20
45 49	215	4	6	7	8	9	10	10	12	14	17	19
50-54	231	4	5	6	8	8	10	10	12	13	15	17
55 59	124	4	5	6	7	8	9	10	11	12	14	15
VELIKA KRSNA YUGOSLAVIA												
40 44	136	4	4	4	4	5	5	6	7	8	10	11
45 49	82	4	4	4	4	5	5	6	7	8	11	14
50 54	135	3	4	4	4	5	5	6	7	8	10	12
55 59	158	3	4	4	4	5	5	6	7	8	12	13

TABLE

Triceps skinfold thickness

AGE	NO MEN	CENTILES 5	10	20	30	40	50	60	70	80	90	95
DALMATIA, YUGOSLAVIA												
40-44	86	4	4	4	5	6	6	8	8	10	12	14
45-49	183	4	4	4	5	6	6	7	8	10	12	13
50-54	211	3	4	4	4	5	6	7	8	9	10	12
55-59	190	3	4	4	4	5	6	6	8	9	12	14
SLAVONIA, YUGOSLAVIA												
40-44	103	3	4	4	5	6	7	8	10	10	14	16
45-49	182	3	4	4	5	6	7	8	10	11	13	16
50-54	197	3	4	4	4	5	6	6	8	10	12	14
55-59	205	3	4	4	4	5	6	6	8	9	11	15
EAST FINLAND (KARELIA)												
40-44	207	3	4	4	5	5	6	7	8	10	14	19
45-49	239	4	4	4	5	6	7	7	9	11	15	17
50-54	197	3	4	4	5	6	6	8	9	12	15	18
55-59	172	3	3	4	5	5	6	7	9	11	14	18
WEST FINLAND												
40-44	168	4	4	5	6	6	7	8	10	11	14	17
45-49	224	4	4	5	6	6	7	8	9	11	13	17
50-54	245	4	4	5	6	6	7	8	10	12	15	17
55-59	222	3	4	4	5	6	7	8	9	10	14	16
CREVALCORE, ITALY												
40-44	174	4	5	6	8	10	11	12	15	17	21	22
45-49	304	4	5	6	7	9	10	12	15	17	20	22
50-54	292	4	6	6	8	9	10	12	13	15	19	21
55-59	220	4	5	6	8	9	10	12	14	17	20	23
MONTEGIORGIO, ITALY												
40-44	123	3	3	4	4	4	6	7	8	9	11	12
45-49	247	3	4	4	4	5	6	6	8	10	12	13
50-54	216	3	4	4	4	5	6	6	8	8	10	12
55-59	129	3	3	4	4	5	5	6	7	8	10	12

TABLE

Triceps skinfold thickness

AGE	NO MEN	CENTILES 5	10	20	30	40	50	60	70	80	90	95
ZUTPHEN NETHERLANDS												
40-44	181	4	6	6	8	8	10	10	12	14	16	18
45-49	237	4	5	6	8	8	9	10	11	12	14	16
50-54	234	4	5	6	8	8	10	10	12	13	15	18
55 59	225	4	6	6	7	8	10	10	11	12	14	16
CRETE GREECE												
40-44	160	3	4	4	4	5	6	6	8	10	13	14
45 49	202	3	4	4	4	5	5	7	8	10	14	20
50-54	175	3	3	4	5	5	6	7	8	10	11	12
55-59	148	3	3	4	4	5	5	6	6	7	9	11
CORFU GREECE												
40 44	120	4	4	4	5	5	6	7	9	10	11	15
45 49	114	3	4	4	4	5	6	7	8	10	12	15
50 54	169	4	4	4	4	5	6	6	8	9	12	16
55 59	126	3	4	4	4	4	5	6	7	10	12	15
ROME ITALY RAILROAD EMPLOYEES												
40-44	196	5	6	7	8	9	10	11	12	14	17	20
45-49	215	4	6	7	8	9	10	10	12	14	17	19
50-54	231	4	5	6	8	8	10	10	12	13	15	17
55 59	124	4	5	6	7	8	9	10	11	12	14	15
VELIKA KRSNA YUGOSLAVIA												
40-44	136	4	4	4	4	5	5	6	7	8	10	11
45 49	82	4	4	4	4	5	5	6	7	8	11	14
50 54	135	3	4	4	4	5	5	6	7	8	10	12
55-59	158	3	4	4	4	5	5	6	7	8	12	13

Prevalence of hypertension Number of men with diastolic blood pressure (fifth phase) of 95 mm or more, and of 100 mm or more N = total men OBS = cases observed cases *expected from the prevalence in all 18 samples* Chi-square value given in parenthesis

SAMPLE	AGE	N	95 or more		100 or more	
			OBS	E	OBS	E
Nicotera	45-49	230	3	38 346	2	22 446
	50-54	123	6	24 531	4	15 995
	55-59	117	7	25 005	5	16 170
	45-59	470	16	87 882	11	54 611
	"		(75 03)		(40 48)	
U S Switchmen	40-44	281	40	41 990	27	24 936
	45-49	243	50	40 513	34	23 714
	50-54	153	34	30 514	23	19 896
	55-59	159	43	33 981	33	21 975
	40-59	836	167	146 998	117	90 521
	"		(N S)		(8 97)	
U S Sedentary Clerks	40-44	167	33	24 955	21	14 820
	45-49	184	39	30 676	22	17 957
	50-54	239	63	47 666	42	31 080
	55-59	268	66	57 277	47	37 040
	40-59	858	201	160 574	132	100 897
	"		(13 20)		(11 37)	
U S Non-Sedentary Clerks	40-44	31	3	4 632	1	2 751
	45-49	39	7	6 502	2	3 806
	50-54	38	14	7 579	11	4 942
	55-59	47	21	10 045	13	6 496
	40-59	155	45	28 758	27	17 995
	"		(10 72)		(4 61)	
U S Executives	40-44	46	6	6 874	4	4 082
	45-49	35	3	5 835	2	3 416
	50-54	71	30	14 160	20	9 233
	55-59	95	20	20 303	13	13 130
	40-59	247	59	47 172	39	29 861
	"		(N S)		(N S)	
Tanushimaru	40-44	112	2	16 736	2	9 938
	45-49	117	4	19 506	4	11 418
	50-54	137	10	27 323	9	15 215
	55-59	143	22	30 562	15	19 764
	40-59	509	38	94 127	30	56 335
	"		(42 18)		(13 91)	
Dalmatia	40-44	83	11	12 403	6	7 365
	45-49	183	27	30 510	16	17 859
	50-54	211	38	42 082	16	27 438
	55-59	193	31	41 248	18	26 675
	40-59	670	107	126 243	56	79 337
	"		(N S)		(8 28)	

SAMPLE	AGE	N	95 or more OBS	95 or more E	100 or more OBS	100 or more E
Slavonia	40-44	102	14	15 242	9	9 051
	45 49	181	31	30 176	20	17 664
	50-54	197	22	39 290	16	25 618
	55 59	217	48	46 377	27	29 992
	40-59	697	115	131 085	72	82 325
			(N S)		(N S)	
East Finland	40-44	206	45	30 783	27	18 280
	45-49	235	64	39 179	41	22 934
	50-54	197	70	39 290	47	25 618
	55-59	170	65	36 332	43	23 496
	40 59	808	244	145 584	158	90 328
			(87 09)		(60 32)	
West Finland	40-44	168	14	25 104	7	14 908
	45 49	224	13	37 345	8	21 860
	50-54	245	36	48 863	25	31 860
	55 59	222	30	47 446	16	30 683
	40 59	859	93	158 758	56	99 311
			(114 28)		(22 54)	
Crevalcore	40-44	164	27	24 507	14	14 553
	45 49	302	62	50 349	31	29 472
	50 54	290	75	57 838	45	37 712
	55 59	228	65	48 728	39	31 512
	40 59	984	229	181 422	129	113 249
			(16 36)		(N S)	
Montegiorgio	40 44	123	7	18 380	3	10 915
	45-49	247	22	41 180	7	24 105
	50 54	217	32	43 278	18	28 219
	55 59	131	20	27 997	11	18 106
	40 59	718	81	130 835	39	80 345
			(24 23)		(24 88)	
Zutphen	40-44	180	53	26 897	35	15 973
	45 49	237	69	39 513	42	23 129
	50-54	233	72	46 470	54	30 299
	55 59	225	71	48 087	51	31 097
	40-59	875	265	160 967	182	100 498
			(88 22)		(79 74)	
Ushibuka	40 44	115	8	17 184	4	10 205
	45-49	128	17	21 340	11	12 492
	50 54	139	18	27 722	12	18 076
	55 59	118	15	25 219	9	16 309
	40 59	500	58	91 465	36	57 082
			(15 19)		(8 75)	

SAMPLE	AGE	N	95 or more OBS	95 or more E	100 or more OBS	100 or more E
Crete	40-44	158	22	23 610	9	14 021
	45-49	201	27	33 511	10	19 616
	50-54	173	19	34 503	11	22 497
	55-59	146	14	31 203	8	20 179
	40-59	678	82	122 827	38	76 313
	"		(17 16)		(22 39)	
Corfu	40-44	120	10	17 932	7	10 649
	45-49	114	17	19 006	10	11 125
	50-54	169	22	33 705	13	21 977
	55-59	126	14	26 929	8	17 414
	40-59	529	63	97 572	38	61 165
	"		(15 28)		(10 40)	
Rome Railway Men	40-44	197	50	29 438	31	17 482
	45-49	215	70	35 845	47	20 982
	50-54	232	61	46 270	43	30 169
	55-59	124	44	26 501	31	17 138
	40-59	768	225	138 054	152	85 771
	"		(70 56)		(60 60)	
Velika Krsna	40-44	136	12	20 322	5	12 069
	45-49	82	8	13 671	3	8 002
	50-54	135	16	26 924	7	17 555
	55-59	158	21	33 768	12	21 837
	40-59	511	57	94 685	27	59 463
	"		(18 75)		(20 34)	

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SAMPLE	AGE	N	95 or more		100 or more	
			OBS	E	OBS	E
Crete	40-44	158	22	23 610	9	14 021
	45-49	201	27	33 511	10	19 616
	50-54	173	19	34 503	11	22 497
	55-59	146	14	31 203	8	20 179
	40-59	678	82	122 827	38	76 313
	"		(17 16)		(22 39)	
Corfu	40-44	120	10	17 932	7	10 649
	45-49	114	17	19 006	10	11 125
	50-54	169	22	33 705	13	21 977
	55-59	126	14	26 929	8	17 414
	40-59	529	63	97 572	38	61 165
	'		(15 28)		(10 40)	
Rome Railway Men	40-44	197	50	29 438	31	17 482
	45-49	215	70	35 845	47	20 982
	50-54	232	61	46 270	43	30 169
	55-59	124	44	26 501	31	17 138
	40-59	768	225	138 054	152	85 771
	"		(70 56)		(60 60)	
Velika Krsna	40-44	136	12	20 322	5	12 069
	45-49	82	8	13 671	3	8 002
	50-54	135	16	26 924	7	17 555
	55-59	158	21	33 768	12	21 837
	40-59	511	57	94 685	27	59 463
	"		(18 75)		(20 34)	

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SUPPLEMENTUM 161

ULTRASOUNDCARDIOGRAPHY IN MITRAL STENOSIS

WITH PARTICULAR REFERENCE TO THE RELATIONSHIP TO HEMODYNAMIC AND SURGICAL FINDINGS

BY

ARNE GUSTAFSON

LUND 1966

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SUPPLEMENTUM 461

FROM THE CARDIOLOGIC CLINIC, DEPARTMENT OF INTERNAL MEDICINE
AND THE DEPARTMENT OF CLINICAL PHYSIOLOGY, UNIVERSITY HOSPITAL, LUND, SWEDEN

ULTRASOUNDCARDIOGRAPHY IN MITRAL STENOSIS

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CONTENTS

INTRODUCTION

In 1954 EDLER and HERTZ (32) described a method for recording of the movements of the heart walls by means of reflected ultra ound, *ultrasound cardiogram* (UCG) Further investiga tions by EDLER (24 25) showed that the UCG curve had a characteristic appearance in mitral steno is the de cent of the curve during diastole was slower than in normal ca e after mitral commissurotomy this movement became more rapid Thus the ultra oundcardiogram could be u ed to e timate the degree of mitral steno is EDLER and GUSTAFSON (29) – The left atrial wall wa at first suppo ed to be the structure giving ri e *to the ultra ound echo with the charac* teri tic movement pattern in mitral teno is Through the studies by EDLER et al (30 31) it was shown that this echo emanated from the anterior mitral leaflet

The value of the UCG in the pre operative evaluation of patients with mitral steno is has since been confirmed by other workers e g EFFERT (33) and JOYNER et al (60) However in mo t report concerning the ultrasoundcardio gram and mitral teno is the dia tolic de cent rate of the UCG-tracing has merely been related to a rough estimate of the size of the mitral orifice at operation

More recently another component of the UCG tracing emanating from the movements of the anterior mitral leaflet ha *proved to be of po sible* value in the preoperative evaluation of mitral steno is, namely the amplitude of the curve from its lowest position in systole to the highest one in early diastole A reduced amplitude in mitral stenosis with calcification of the leaflets was found by EDLER in 1963 (27)

The aim of the present investigation was to evaluate more completely the place of the ultrasoundcardiogram in the preoperative examination of patients with mitral valvular disease For this purpo e the UCG-findings were related to the following findings in a series of patients with mitral stenosis

1) Data from routine clinical exam ination including a essment of the *functional di ability by history and* work test

2) Hemodynamic data obtained by right heart catheterization at rest and during exerci e including the mitral valve area calculated by the Gorlin formula

3) Surgical findings at mitral com missurotomy The mitral valve area was accurately determined and the mobility of the mitral leaflets and the degree of calcification of the mitral valve were estimated A statistical evaluation was performed of the relation of the diastolic descent rate and the maximal amplitude of the UCG tracing to these finding

Finally three estimates of the degree of mitral steno is namely the de cent rate of the UCG the calculated mitral valve area and the surgeon s estimate of the valve area were correlated to the clinical and hemodynamic data the

coefficients of correlation for the three estimates of the degree of stenosis were compared

In addition a methodological study of UCG was performed The reproducibility of the method, the effect of heart rate, of different heart rhythms (sinus rhythm and atrial fibrillation) and the effect of respiration upon the UCG-tracing were evaluated

CHAPTER 1

MATERIAL

Seventy one patients with disease of the mitral valve judged as predominant mitral stenosis were studied. All patients were subsequently operated upon and an attempt was made to estimate the mitral valve area and the mobility of the leaflets as exactly as possible during the operations. The operations were performed during the period May 1963 to September 1964.

There were 42 women with a mean age of 46.1 years, range 29–61 years, and 29 men, mean age 37.1 years, range 30–60 years. Thirty nine patients with a mean age of 43.6 years had sinus rhythm and thirty two with a mean age of 49.9 years had atrial fibrillation; the difference between the mean ages was statistically significant ($p<0.01$).

A history of rheumatic fever or chorea minor was noted in 44 patients. The average length of time between the first known occurrence of rheumatic fever and operation was 31 years (range 5–59 years).

In four patients the diagnosis was restenosis after an earlier digital mitral commissurotomy.

Before operation 42 patients had an apical systolic murmur which could be a sign of some degree of mitral insufficiency. In 6 patients this murmur was pansystolic in time, in 11 patients it occupied 3/4 of systole, the remaining 25 had only a short early systolic murmur.

Physical signs of concomitant aortic valvular disease, i.e. a systolic murmur of crescendo decrescendo type in the second right intercostal space and/or an early high pitched diastolic murmur at this site and along the left sternal border were found in 19 patients. Of these patients 6 had signs of combined aortic stenosis and insufficiency, 3 of aortic stenosis and 10 of aortic insufficiency.

One patient, No 84, had an arterial hypertension which had been under treatment for the past six years. Six additional patients had an arterial blood pressure which was higher than 150/90 mm Hg, in only one of them the diastolic blood pressure was more than 100 mm Hg.

Patient No 84 with arterial hypertension was the only one in the whole material having definite electrocardiographic signs of left ventricular hypertrophy, i.e. a ventricular activation time of ≥ 0.05 sec and $R_{V_5} - S_{V_1} \geq$ 35 mm.

The degree of functional capacity was assessed according to the clinical grades of the New York Heart Association (74) with the modification used by BISHOP and WADE (8). Three patients belonged to group I, all with sinus rhythm, 24 to group II, 21 with sinus rhythm and 3 with atrial fibrillation, 29 to group III A, 12 with sinus rhythm and 17 with atrial fibrillation; the remaining 15 patients belonged to group III B, 3 with sinus rhythm and 12 with atrial fibrillation.

CHAPTER II

METHODS

CLINICAL EXAMINATION

The patients were admitted to the Cardiologic Clinic during the preoperative examinations which usually were performed one to four weeks before the operation. In order to include all relevant data the *history* was taken according to and recorded on a form especially prepared for the present study.

Besides routine physical examination a 12 lead *electrocardiogram* and *phonocardiogram* were recorded in all patients. A four channel direct writing ECG apparatus (Mingograph 42, Elema Schönander AB) was used for these examinations. The following ECG leads were used: I—III, aVR, aVL, aVF and chest leads V_{1-6}. Phonocardiograms were recorded from the apex, the fourth and second left and the second right intercostal spaces. The frequency bands with a nominal frequency of 25, 100 and 400 c/s were used at all recordings.

ROENTGENOLOGICAL EXAMINATION

Chest radiograms were taken in the frontal and the lateral projections with the patient in the standing position, the oesophagus was filled with contrast. The *heart volume* was determined according to the method of JONSELL (58).

Cine fluorography was performed on all patients to demonstrate possible calcifications of the mitral valve; the examination was performed in the right anterior oblique and the lateral projections.

EXERCISE TEST

The exercise test was performed with the patient in the sitting position on an electrically braked cycle ergometer HOLMGREN and MATTSSON (53). Successively increasing work loads, multiples of 200 kpm/min for women and 300 kpm/min for men, were used according to the principles described by SJÖSTRAND (89).

The ECG was continuously observed on an oscilloscope and recorded every second minute on each load. Heart rate was calculated from the ECG. The respiratory frequency was also counted. The work load was not increased until a steady state had been reached. Steady state was considered to exist when the difference in heart rate between two successive observations was smaller than 5 beats/min. The exercise test was stopped when the heart rate reached 170 beats/min or when multiple ventricular extrasystoles appeared or because of excessive fatigue or dyspnea.

HEART CATHETERIZATION

Right heart catheterization was performed in 69 patients. In two patients with sinus rhythm atrial fibrillation occurred during the examination, the hemodynamic data from these two patients were omitted. Thus data from right heart catheterization were available for 67 patients.

Technique. The catheterizations were performed in the morning, the patients were not given breakfast. As premedication 0.10—0.15 g pentobarbital was given.

The heart catheter was introduced through a cubital vein and passed to the pulmonary artery and pulmonary arterial wedge position under fluoroscopic control.

The catheters were radiopaque (U.S. Catheters & Instr. Corp.); in 19 examinations a single lumen catheter, as a rule No. 7, was used, in the others a double lumen catheter No. 9.

A polyethylene catheter was inserted in the brachial artery by the percutaneous technique of SELDINGER (86). In three patients the arterial puncture was unsuccessful, hence determinations of cardiac output could not be performed in these patients.

An exercise test in the supine position was performed after the measurements at rest in all but seven patients: six of these patients had orthopnea at rest and one (case 98) a bundle branch block which appeared during the catheterization. The exercise data in case 136 were omitted because of a technical error (too small a load on the bicycle in relation to the dial setting).

Three different bicycle ergometers were used

An older type of mecha ically braked bicycle was used at four exan inations (cases 39 9 81 and 83) determinat ons of the oxygen consump tion during exerc e cn this b cycle n a larger series of pat ents showed that the work load corresponded to about 200 kpm m n Another type of n echanically braked b cycle ergometer des gned by VON DOBELN (23) (KIFA AB) was u ed n most of the exerc se tests The load was adjusted so that the work inten ty was 200 or 300 kpm m n when the pat ent was pedall ng at a constant rate of 50 c/min Finally in the la t 22 exam nat ons (cases 1 101 and 131—158) the above t er t oned electrically braked ergo meter was u ed with a work load of 200 kpm min for wo nen and 300 kpm n n for men

DETERMINATION OF CARDIAC OUTPUT Car I ac output was usually simulta eou ly determi ed by the d rect Fick method and by the i d ca t r d lut on method at rest a d during exerci e However in 10 cases o ly the indicator d lut on techn que was used and in 5 cases only the Fick method

F k m thod The exp red a r was collected for 7 n utes in a Douglas bag when card ac output was determ ed at re t The bag had prev ou ly been r nsed with the pat e t s exp red a r After 3 m nutes of air collect on the i d cator was injected a d blood collected n the Eller a n tubes as descr be l below Immed ately after th s 8 10 r l sa ples were s multaneou ly drawn fr n the pulm onary and brachial arteries to all gla s syringes mo tered w th I epar n Finally an arterial blood sa nple was drawn for deter nation of the hen atocr te value and the he glob n c centrat on

Dur g exercise the exp red a r was as a rule collected f r 4 m nutes The collect on started when the pat ent had bee pedall ng at a con tant rate f r three m nutes After about two m nutes f a r s pl ng the ind cator was njected a d blood sa ples draw as descr bed above

Before the em pty ng through the gas meter nall port ons of the collected a r were trans ferred to gas rec p ents The e samples were then analyzed w th a SCHOLANDER apparatus (84) Vent lation n l n n (BTPS) and oxyge c n un pt on in l n n (STPD) were calculated

Oxygen saturat on and oxygen capac ty of the blood samples were determined by a spectro ph ton etr c method as described by HOLMGREN and LINNOW (54) and the arterio-ven ous oxygen d ffere ce wa calculated

Ind cator d lut on method Bro nsulphale n (BSP) wa used a ind cator accord ng to WA SEN (93). Exactly 10 ml of a 1.5 per cent BSP-solution in phy iolog cal sal ne was rapidly injected nto the pulmo ary artery by hand w th an all gla s Luer Lok syr ge Immed ately after the injection 2 3 ml was w thdrawn from the catheter with the san e syringe. The blood collection from the catheter in the brachial artery started at the san e time as the injection. A rotating d e with 40 heparinized tubes driven by a synchronous motor was u ed for the collect on The collection time was 1 second per tube except in a few pat ents with very low rate of flow when the t me was 2 seconds per tube The lo s of blood through the sampling was 15—20 cc.

The Ellermann tubes were centrifuged for 15 n nutes at 4000 r per min 0 1 ml serum was drawn from each tube a d added to 3 n l alkal ne buffer olution in a cuvette (for com position of the buffer solut on see FORSBERG (4?)) The extinction was read in a Beckman B spectro-photometer at a wave length of 580 mμ Then BSP was discoloured by add ng of 0 1 ml of an ac dify ng solution see FORSBERG (42) and the extinct on was determined aga n t water as a blank The last ext nction value was subtracted from the first one

The extinction value of the BSP olution u ed for the inject on was determ ned in the following way 1 n l of the solut on was d luted w th 2 0 ml di tilled water and the ext nction of 0 1 ml of th s solut on was determ ed as descr bed above Th s procedure was repeated as a control with 1 ml of the BSP solut o d luted in 500 r l distilled water

The flu d w thdraw n from the catheter after each nject on was d luted w th distilled water to 250 n l and the ext nct on of 0 1 ml was determ ed as described above

The ext nction value of the BSP in the syr nge minus the ext nct on value of the flu d withdrawn represented the quant ty of BSP njected into the pat ent

The hematocr te value was determ ned by centrifu ng an arterial blood sample for 5 m utes in a he atocr te centr fuge (Ken la Stockh lm)

The extinction values of the samples in the Ellermann tubes were plotted on a semi logar thmic paper The stra ght descer ding sect on of the curve was extrapolated after the po nt where the rec rculat on wave appeared down to the basal level

Card ac output was determ ned by the following formula

$$CO = \frac{60 \cdot I \cdot 100}{T \cdot \Sigma X \cdot (100 - H)}$$

where CO card ac output n l m n.
I — BSP injected in ext nct on un ts
T = collection t me per tube
ΣX the sum of the extinction values on the curve w th n the area of extrapolation
H hematocrite

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Three different bicycle ergometers were u ed

ated during two sampling periods in immediate succession the interval between the mentioned determinations was about seven minutes

Table 1 *Duplicate determinations at rest*

	n	Mean I	Mean II	Mean diff I—II	$\pm$ S E of mean diff	P	$\sqrt{\frac{\Sigma d^2}{2n}}$ (% of mean value)
Heart rate (beats/min)	27	72 0	71 3	0 7	0 59	>0 20	2 16 (3 0)
Cardiac output BSP (l/min)	26	4 80	4 72	0 09	0 10	>0 30	0 36 (7 5)
Stroke volume BSP (ml beat)	26	0 2	69 7	0 42	1 27	>0 70	4 5 (6 4)
Cardiac output FICK (l min)	12	5 25	5 20	0 05	0 20	>0 80	0 47 (9 0)
Stroke volume FICK (ml/beat)	12	76 8	76 0	0 75	2 55	>0 80	6 0 (7 8)
Oxygen consumption (ml min STPD)	12	234	229	5 3	6 6	>0 40	16 0 (6 8)
A V oxygen difference (ml l)	26	53 6	53 2	0 43	0 62	>0 50	2 2 (4 1)
Mean pressures mm Hg							
Brachial artery	24	95 3	95 2	0 1	0 5	>0 80	1 7 (1 8)
Pulmonary artery	25	23 6	23 6	0 08	0 49	>0 80	1 7 (7 2)
Pulmonary arterial wedge	21	15 8	15 0	0 81	0 57	>0 10	1 9 (12 3)

The results are shown in table 1 No variable showed any significant difference between the first and second determination The standard error of a single determination was 8 % when cardiac output was estimated with BSP and 9 % when the Fick method was used

Comments The methodological error for determination of cardiac output with the Fick method in the present study was of the same order as that found by other investigators e g DONALD et al (22) THOMASSON (90) HOLMGREN and PERNOW (54) WERKO (96) SAMET et al (83)

The error of duplicate determinations with BSP was of the same order as that reported by FORSBERG (42)

Examinations during exercise

The reproducibility of the measurements of cardiac output and of pressure recordings during exercise was studied in 23 catheterizations *performed by the* author All the patients had mitral valvular disease 14 had sinus rhythm and 9 atrial fibrillation Eight catheterizations were performed before operation in patients included in the present material while 15 were postoperative examinations

The work load was generally 300 kpm/min for men and 200 kpm/min for women Cardiac output was simultaneously measured with BSP and Fick methods as previously described The first gas sampling period was between the third and seventh minute of work after the Douglas bag had been exchanged the expired air was collected for another 4 minute period (during about 7.5 to 11 5 minutes of work) The BSP determination and blood sampling for estimation of the arterio venous oxygen difference was started about two minutes after the beginning of each gas sampling period Pressures were recorded immediately before each BSP injection and heart rate was calculated as previously described

PRESSURE RECORDING Blood pressures were measured with a pressure transducer of variable inductance type connected to an electronic unit (EMT 460 Elema Stockholm) except in the last 22 examinations when a transducer of capacitance type (EMT 34 or 35) with electromanometer (EMT 31) was used The pressure tracings were recorded with direct writing electrocardiographs, in the former case Mingograph 42 in the latter Mingograph 81

The paper speed was 50 mm/s when undamped tracings were recorded and 5 mm/s for mean pres ures Systolic and diastolic pressures were measured over 7—10 heart cycles, corresponding to at least one respiratory cycle, and the mean value of these measurements for each pressure was noted Mean pressures were recorded by means of electrical integration

The reference level for all pressures was 5 cm below the sternal angle the position of the transducer was checked with a water level

For the recording of right heart pressures only one transducer was used rotating adapters were used for the connections The polyethylene catheter in the brachial artery was connected to another tran ducer

The electromanometer recording right heart pressures was calibrated with the pressure from an elevated bottle with physiological saline except when calibration pressures higher than 70 mm Hg were needed then a mercury mano meter was used The latter was always used for calibration of the electromanometer recording systemic arterial pressures Zero level and calibration pressure were always recorded before and after each pressure tracing At the end of the examination the linearity of the pressure recording system was checked with calibration pressures at different levels

At rest right heart and brachial arterial pressures were recorded immediately before and after the determinations of cardiac output (the pressures listed in the tables were those recorded before the determination of cardiac output) When a double lumen catheter was used the mean pressures in the pulmonary arterial wedge position and in the pulmonary artery were recorded in immediate succession by switching the stopcock on the transducer When a single lumen catheter was used the mean pressure in the wedge position was recorded first and then the mean pressure in the pulmonary artery after withdrawal of the catheter

During exercise right heart and systemic arterial pres ures were recorded each minute from the moment the patient started pedalling at a constant rate If a double lumen catheter was used the mean pres ures were recorded as described above the pressures denoted as exercise pre sures in the tables were generally recorded after 4—4 5 minutes of work immediately before the determination of cardiac output When a single lumen catheter was used the mean pressure in the wedge position was recorded each minute for the first three minutes of work, then the catheter was withdrawn and the mean pressures in the pulmonary artery recorded immediately Before the patient stopped working the catheter was withdrawn to the right ventricle and to the right atrium and the pressures in these heart chambers were recorded

The pressure at rest in the right atrium was recorded 5—10 minutes after the exercise test

During determination of cardiac output at rest and during exerci e the Mingograph was continuously recording the ECG with a paper speed of 5 mm/s the heart rate was then calculated by counting the R waves over one minute

REPRODUCIBILITY OF DETERMINATIONS OF CARDIAC OUTPUT AND PRESSURES AT REST AND DURING EXERCISE THE RELATIONSHIP BETWEEN CARDIAC OUTPUTS DETERMINED SIMULTANEOUSLY BY FICK AND BSP METH ODS

Examinations at rest

Duplicate determinations of cardiac output and pressures at rest were per formed in 27 patients with mitral valvular disease selected at random Nineteen patients had sinus rhythm and 8 had atrial fibrillation The catheteriza tions were performed by the present author by the technique described above Fourteen examinations were made before operation, 10 of these patients were included in the pre ent material, and 13 were performed one year after mitral valvulotomy

Duplicate determinations of cardiac output with BSP and of arterio venous oxygen difference were performed at 26 catheterizations, in 12 of these duplicate determinations of oxygen consumption were also performed which made dup licate Fick determinations possible

The time interval between the two measurements was about three minute when only cardiac output with BSP arterio venous oxygen difference and pressures were determined in duplicate when oxygen consumption was estim

ated during two sampling periods in immediate succession the interval between the mentioned determinations was about seven minutes

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The error of duplicate determinations with BSP was of the same order as that reported by Forsberg (42)

Examinations during exercise

The reproducibility of the measurements of cardiac output and of pressure recordings during exercise was studied in 23 catheterizations performed by the author All the patients had mitral valvular disease 14 had sinus rhythm and 9 atrial fibrillation Eight catheterizations were performed before operation in patients included in the present material while 15 were postoperative examinations

The work load was generally 300 kpm/min for men and 200 kpm/min for women Cardiac output was simultaneously measured with BSP and Fick method as previously described The first gas sampling period was between the third and seventh minute of work after the Douglas bag had been exchanged the expired air was collected for another 4 minute period (during about 7 5 to 11 5 minutes of work) The BSP determination and blood sampling for estimation of the arterio venous oxygen difference was started about two minutes after the beginning of each gas sampling period Pressures were recorded immediately before each BSP injection and heart rate was calculated as previously described

The results are shown in table 2. The mean heart rate and oxygen consumption increased from the first to the second determination, since the cardiac output was practically unchanged the stroke volume decreased. The arterio-venous oxygen difference remain unchanged. All pressures showed higher

Table 2. *Duplicate determinations during exercise*

	n	Mean I	Mean II	Mean diff I—II	± S.E. of mean diff	P	$\sqrt{\frac{\Sigma d^2}{2n}}$	(% of mean value)
Heart rate (beats/min)	23	103.1	106.0	—2.9	0.62	<0.001	—	
Cardiac output BSP (l/min)	23	7.90	7.85	0.05	0.18	>0.80	0.59	(7.5)
Stroke volume BSP (ml/beat)	23	78.7	76.0	2.74	1.84	>0.10	6.4	(8.1)
Cardiac output Fick (l/min)	23	7.96	7.93	0.03	0.18	>0.90	0.59	(7.4)
Stroke volume Fick (ml/beat)	23	79.1	76.8	2.26	1.75	>0.20	6.0	(7.7)
Oxygen consumption (ml/min STPD)	23	739	744	—5.0	14.3	>0.70	47.5	(6.4)
A-V oxygen difference (ml/l)	23	96.8	96.8	0.04	1.70	>0.80	5.6	(5.8)
Mean pressures mm Hg								
Brachial artery	21	107.6	105.9	1.7	1.0	>0.05	3.4	(3.2)
Pulmonary artery	23	35.3	34.6	0.74	0.50	>0.20	1.7	(4.8)
Pulmonary arterial wedge	21	22.4	20.3	2.10	0.45	<0.001	—	

mean values at the first determination than at the second one. However, the increase in heart rate and the decrease in pulmonary arterial wedge pressure were the only differences of any statistical significance.

The standard error of a single determination for measurements of cardiac output was the same with BSP and Fick methods, 0.59 l or 7.5 per cent. The same figure was obtained for duplicate measurements by the BSP-technique at rest while that of the Fick determinations at rest was a little higher. The percentile errors for determinations of oxygen consumption and of arterio-venous oxygen difference were of the same order as those found at rest.

Comments. Donald et al. (21) found that cardiac output in normal subjects achieved a steady state after 1½ minutes of exercise.

Holmgren and Pernow (55) studied the reproducibility of cardiac output measured by the Fick method during exercise in a material of 27 cases which included normal subjects, patients with pulmonary disease and with various heart diseases. The impairment of the cardiac function in that material was less than in the present one, the average cardiac output was higher, 11.1 l/min and the arterio-venous oxygen difference lower, 73 ml/l, at an average oxygen consumption of the same order as in the present material. The work load ranged between 100 and 600 kpm/min. The periods of gas collection and the times for blood sampling were almost identical with those of the present study. The heart rate increased significantly between the two determinations as in the present study, however both the oxygen consumption and the cardiac output also showed a small but statistically significant increase. The reproducibility of all determinations was increased in comparison with duplicate determinations at rest.

Ekelund and Holmgren (36) studied

the circulatory adaptation in 6 normal subjects during long term exercise in a non steady state in the sitting position. Between the 10th and 20th minutes of work they found an increase in heart rate, arterio venous oxygen difference and oxygen consumption. The cardiac output was fairly unchanged during this period while the stroke volume as well as the brachial arterial and pulmonary arterial mean pressures decreased. These circulatory changes were considered to be due to a decrease in the central blood volume.

ELIASCH (37) studied the variations of the pressures in the pulmonary circulation during exercise. He also found a small but statistically significant decrease in the pulmonary arterial wedge pressure from the 3rd to the 7th minutes of exercise. The pulmonary arterial pressure was not recorded simultaneously; it did not show any significant change between the 7th and 12th minutes of exercise. After comparison with duplicate determinations at rest ELIASCH concluded that 'factors other than technical errors played a lesser role during effort than at rest'.

WERKO (96) emphasized that an usual source of error in many studies concerning the hemodynamics of mitral stenosis 'has been the short bouts of exercise during which pressures have been recorded and blood samples taken' and that 'no valid conclusions can be drawn when values for different circulatory parameters are obtained during a state of continuous changes'.

In the present study pressures and flows were recorded after 4—5 minutes of exercise. The results of the duplicate determinations make it evident that most circulatory parameters had achieved a steady state at this time. This recording procedure implied an exercise test of about seven minutes duration which even patients with more advanced stenosis could sustain at the work loads used in the present study.

The relationship between cardiac outputs simultaneously determined by the Fick and the indicator dilution methods

The results of determinations of cardiac output by Fick and BSP methods simultaneously in the present material of 71 patients with mitral valvular disease are shown in table 3 and fig. 1.

Table 3. *Cardiac output determinations simultaneously performed by Fick and BSP methods*

	n	Cardiac output (l/min mean value)		Mean diff Fick-BSP	± S.E. of mean diff	P	$\sqrt{\frac{\Sigma d^2}{2n}}$ (% of mean value)	
		Fick	BSP					
Sinus rhythm								
Rest	3[illegible]	5.67	5.74	−0.07	0.21	>0.80	0.83	(17)
Exercise	31	9.07	8.77	0.31	0.29	>0.20	1.14	(13)
Atrial fibrillation								
Rest	21	3.[illegible]6	3.91	−0.16	0.21	>0.40	0.66	(1[illegible])
Exercise	20	6.37	6.23	0.15	0.26	>0.50	0.81	(13)

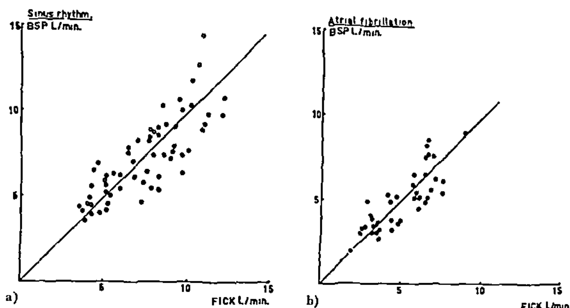

Fig 1 The relation between cardiac output simultaneously determined by BSP and Fick methods at rest and during exercise in patients with sinus rhythm (a) and with atrial fibrillation (b) The line of identity is shown

In patients with sinus rhythm 31 simultaneous determinations were performed at rest and 31 during exercise, in patients with atrial fibrillation the number of determinations was 20 and 21 respectively

In no group of determinations was the mean difference between Fick and BSP values statistically significant The divergence between the two methods calculated by *the formula for the* standard error of a single determination was between 13 and 17 per cent of the mean values of cardiac output in the respective groups These figures were about twice those for the errors of the Fick and BSP methods at duplicate determinations

The correlation between the values obtained by the two methods was higher at rest than during exercise, both in patients with sinus rhythm and in those with atrial fibrillation It was statistically highly significant in patients with sinus rhythm both at rest and during exercise while *in patients with atrial fibrillation* the correlation was significant at rest but only probably significant during exercise (table 3 a)

Table 3 a. *Correlation between Fick (x) and BSP (y) determinations*

	Regression equation	$S_{y \cdot x}$	r	P
Sinus rhythm				
Rest	$y = 2.50 + 0.572x$	1.00	0.731	<0.001
Exercise	$y = -0.07 + 0.974x$	1.68	0.608	<0.001
Atrial fibrillation				
Rest	$y = 0.96 + 0.786x$	0.98	0.635	<0.01
Exercise	$y = 1.42 + 0.755x$	1.42	0.506	<0.05

Comments The agreement between determinations of cardiac output simultaneously performed by the Fick and indicator dilution methods has been studied in several investigations, for a survey of this subject reference should be made to WADE and BISHOP (92) Most authors have not found any systematic difference between the values obtained by the two methods Thus ELIASCH et al (38) in a study of 352 simultaneous determinations found "a fair and similar agreement between the two methods However, at cardiac output levels between 9 and 11 l/min the values obtained by the Fick method were somewhat higher

FORSBERG (42) compared cardiac outputs simultaneously determined by these methods in 23 patients The values obtained by the indicator dilution method were an average of simultaneous determinations with BSP and cardio green The mean value of cardiac output by the dye method was 5 23 l/min and by the Fick method 5 34 l/min The coefficient of correlation was 0 94 and Sy x 0 55 l/min Thus the agreement between the methods was closer than in the present study

THE VASCULAR RESISTANCES IN THE PULMONARY AND THE SYSTEMIC CIRCULATION

The *pulmonary vascular resistance* was calculated by the following formula

$$R = \frac{PA_m - PAW_m}{CO}$$

where

R = resistance in arbitrary units

PA_m = mean pulmonary arterial pressure mm Hg

PAW_m = mean pulmonary arterial wedge pressure mm Hg

CO = cardiac output l/min (Fick value or when this was missing, BSP value)

The *systemic vascular resistance* was calculated by the formula

$$R = \frac{BrA_m}{CO}$$

where

BrA_m = brachial arterial mean pressure mm Hg

THE MITRAL VALVE AREA

The mitral valve area was calculated in 44 patients with no or the slightest degree of mitral insufficiency at operation The formula of GORLIN and GORLIN (44) was used

$$MVA = \frac{MVF}{31 \times \sqrt{PAW_m - 5}}$$

where

MVA = mitral valve area in cm²

MVF = mitral valve flow in cc per sec $\left(\frac{\text{CO in cc per min}}{\text{Diastolic filling period in sec per min}}\right)$

PAW_m = mean pulmonary arterial wedge pressure

5 = assumed value for left ventricular diastolic pressure

31 = an empirically measured constant

The cardiac output determined by the Fick method was used for the calculation in all except three patients where only BSP values were available The diastolic filling period was measured from the brachial arterial pulse pressure tracing, from the catacrotic incisure to the beginning of the upstroke of the next pressure pulse The average value was calculated from 5 cardiac cycles in patients with sinus rhythm and from 10 cycles in patients with atrial fibrillation

Whenever possible the mitral valve area was calculated from both rest and exercise data and the mean value of the two determinations used for the correlation with other parameters

SURGICAL TECHNIQUE

Mitral commissurotomy was performed by means of transventricular dilatation according to LOGAN and TURNER (69) under controlled hypotension with Arfonad, BJORK et al (10)

The patients with atrial fibrillation were treated with dicoumarol for at least three weeks before the operation

Before the dilatation of the valve the surgeon introduced his ungloved finger into the left atrium and the degree of regurgitation, the mobility of the leaflets, the degree and localization of calcifications and the size of the mitral orifice were estimated The author was present at each operation and recorded the surgeon's report

The regurgitation, the mobility of the anterior leaflet and the calcifications were graded as follows

Degree	*Regurgitation*	*Mobility*	*Calcification*
0	No regurgitation	Immobile	No calcification
+	Regurgitant jet palpable not more than one finger (terminal phalanx) from the mitral orifice	Slight mobility	Small localized calcification
++	Jet palpable not more than two fingers from the orifice	Moderate mobility	Larger localized calcification
+++	Jet palpable three fingers or more from the orifice	Good mobility	Extensive calcification (involving both leaflets and commissures)

Hypotension was then induced and dilatation performed to an average measure of 39 7 mm on the dilator (range 38—43 mm) When the blood pressure had reached the same level as before the induction of hypotension the finger was again inserted into the atrium and the findings of palpation were recorded in the same way as at the initial exploration

Immediately after the operation the surgeon shaped a copper wire (except in cases 79 and 81 when modelling clay was used) to a figure of a size and form corresponding to the mitral orifice as it was estimated at palpation, fig 2 This figure was transferred to a millimeter paper, the mitral valve area could then be calculated by counting the millimeter squares enclosed by the tracing

The reproducibility of the estimation of the mitral valve area

At ten operations two surgeons independently of each other explored the mitral valve and estimated the orifice area by the above mentioned method in order to test its validity [1]

The results of these comparisons is shown by fig 3 The mean value of the differences between the estimated valve areas was 0 26 cm², range 0 01—0 61 As shown by the figure a systematic difference was found between the two surgeons' estimates in valve areas about 2 cm², where the ostium was larger than the palpating finger the valve areas calculated from the wires shaped by "surgeon 1" were always larger than those estimated by "surgeon 2" the mean difference was 0 41 cm² The cross sectional area of the index finger of "surgeon 1" at the basis of the terminal phalanx was 1 8 cm², that of "surgeon 2" was 1 7 cm² However when the finger, or part of it, occluded the orifice the difference between the surgeons estimates was less thus it averaged

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[1] The author is indebted to Drs Olle Dahlback and Jan Kugelberg who performed the operations

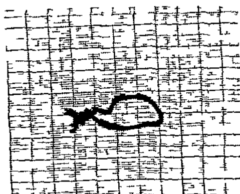

Fig 2 *The surgeon s estimate of the mitral valve area*

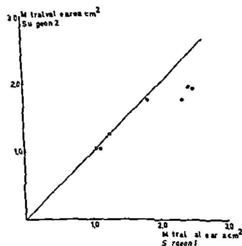

Fig 3 *The relation between two surgeons estimate of the mitral valve area The line of identity is shown*

0 04 cm² in areas of 1 5 cm² or less in size

Comments The size of the mitral orifice has been expressed in different ways The length and the width of the orifice has often been used e g by BROCK (14) who found that the mitral orifice in mitral stenosis is almost always a small oval about 1 cm × 0 5 cm The area has been expressed in square centimeters e g by GORLIN and GORLIN (44) DEXTER et al (17) stated 1 2 cm² as the "critical narrowing of the mitral valve" and that symptoms usually appeared first when the mitral valve area was about 1 5 cm² or less in size

The method of estimating this area at operation has but seldom been described HARLEY (50) used a "mitral measure of plastic and KULKARNI et al (63) a 'gloved waxtipped finger by which a wax impression of the mitral orifice was taken, this was frozen and subsequently measured

The part of the surgeon s finger which the orifice admits is probably the method most often used to express the mitral valve area LOGAN et al (68) used this method and refrained from stating a measurement in square centimeters or in diameter length "to avoid a false appearance of precision GRANATH (45) considered too detailed a classification based on mitral area estimated at operation to be of small value and graded the mitral stenosis as 'less tight and "tight depending upon whether the mitral orifice did admit the surgeon s finger or not

The 'finger measure gives only a very approximate measure of the mitral valve area partly due to different sizes of the palpating fingers This is evident from the investigations in which besides the finger measure , the cross sectional area of the terminal phalanx of the surgeon s finger has been reported e g 1 3 cm² by WASSERMIL et al (94) and 2 0 cm² by MALERS (70) BADEN (5) considered that Brock s 'standard orifice of 1 0 × 0 5 cm corresponded to one of 'terminal phalanx size But this length and width of the ostium corresponds to an area of 0 4 cm² on HARLEY s 'mitral measure (50)

The difficulties in estimating the mitral valve area at post mortem examination have recently been discussed by RICHTER (79) who found a range between 1 4 and 2 0 cm² in one

case, depending on the method used for the measurement

The method used in the present study showed a good agreement between the estimates of two surgeons when the finger could occlude the orifice The *difference was* greater but the agreement still relatively good when the finger could be moved within the orifice KULKARNI et al (63) also considered that the estimated mitral valve areas in such cases were "necessarily approximate"

No attempts were made in the present series at estimating the area in square centimeters after dilatation of the valve BAILEY et al (7) also considered such attempts to be unsatisfactory

STATISTICAL METHODS

Conventional statistical methods were used, e g DIXON and MASSEY (20) Differences between means were tested by the t test and analysis of variance, the t-test was also used for testing whether a correlation coefficient differed from zero The hypothesis that two samples represent the same theoretical population was tested by Wilcoxon's rank sum test

The following probability (P) levels of significance were used

Probably significant
$0\ 01 < P \leq 0\ 05$ (denoted by *)
Significant
$0\ 001 < P \leq 0\ 01$ (denoted by **)
Highly significant
$P < 0\ 001$ (denoted by ***)

The calculations in the statistical evaluation of the data were partly performed with the use of the electronic computer SMIL at the Institute of Numerical Analysis, Lund

ULTRASOUNDCARDIOGRAM

METHOD

THE APPARATUS AND THE RECORDING UNIT

The equipment used was an ultra ound reflectoscope manufactured by Siemens Reiniger Werke Germany For a detailed description of the equipment see EDLER (26)

All UCG-tracings in the pre ent study were recorded by the direct writing method described by EFFERT HERTZ and BOHME (35) In this method a converter is used to transform into voltage fluctuations the time elapsing from the emission of the sound pulse from the crystal to the echo return These voltage changes can be recorded by an electrocardiograph (in the present study a direct writing Mingograph 42 Elema Stockholm was used)

Electrocardiogram and phonocardiogram were always recorded simultaneously with the UCG

THE CRYSTAL AND THE FREQUENCY OF THE ULTRASOUND

A barium titanate crystal with a diameter of 12 mm and a frequency of 2 5 Mc/s (max impul e inten ity 40 watts/cm²) was u ed for all recordings in the present study The relative merits of different frequencies of ultrasound have been di cu sed by EFFERT (33) and by EDLER (26) Ultra ound with a lower frequency e g 1 Mc/s has a better penetrating power but its resolving power is lower than at the frequency of 2 5 Mc/s In the present series the penetrating power of the latter frequency was sufficient to obtain sati factory tracings in all the patients

THE PERFORMANCE OF THE RECORDING

The recordings were performed when the patient was lying down with the chest elevated about 20 degrees The patient was not instructed to hold the breath while the recording was performed but was breathing normally

Whenever possible recordings were made from both the 3rd and 4th costal interspaces at varying distances from the midsternal line The latter distance was determined by the possibility of obtaining satisfactory tracings At the recordings the crystal was held as vertically as possible extreme inclinations were avoided

Before each examination the amplification of the Mingograph was adjusted with the test plug of the ultrasound apparatus This test plug was originally de cribed by EFFERT HERTZ and BOHME (35) It con ists of a piece of aluminium with a piezoelectric crystal attached to one end the time taken for an ultrasound impulse to pass from the crystal to the opposite end and back corresponds to that taken for the impulse to traverse 2 cm of blood back and forth The amplifier of the electrocardiograph was adjusted so that the distance between the echoes produced

case, depending on the method used for the measurement

The method used in the present study showed a good agreement between the estimates of two surgeons when the finger could occlude the orifice The difference was greater but the agreement still relatively good when the finger could be moved within the orifice KULKARNI et al (63) also considered that the estimated mitral valve areas in such cases were "necessarily approximate"

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STATISTICAL METHODS

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The following probability (P) levels of significance were used

Probably significant
$0.01 < P \leq 0.05$ (denoted by *)
Significant
$0.001 < P \leq 0.01$ (denoted by **)
Highly significant
$P < 0.001$ (denoted by ***)

The calculations in the statistical evaluation of the data were partly performed with the use of the electronic computer SMIL at the Institute of Numerical Analysis, Lund

descent rate between individual heart cycles was caused by artifacts when the recording was performed during breath holding The range was not larger in patients with atrial fibrillation than in those with sinus rhythm The same author mentioned that this range was also valid for the *reproducibility* of repeated recordings

EDLER (26) when studying the descent rate discussed the errors inherent in changes in the sweep velocity of the electron beam, in the amplitude of the *echo* signal and in the time factor When the direct writing method was used be found that the total error inherent in these factors was "11 % at most

JOYNER, REID and BOND (60) stated that many of their patients had ultrasound recordings repeated on different days with consistently similar curves and calculated velocities"

No statistical evaluation has however been published of the validity and reproducibility of the two parameters descent rate and maximal amplitude which were measured in the present study

The UCG tracings used for the present study were all recorded in patients with mitral stenosis before or after commissurotomy

THE VARIATION DURING CONTINUOUS RECORDING

Eighty three UCG tracings from 18 patients were used for this study Twelve patients had sinus rhythm 5 had atrial fibrillation and in one patient UCG was recorded both in sinus rhythm and in atrial fibrillation (table 4)

In the patients with sinus rhythm the mean value of the descent rate was 15 1 mm/s and that of the maximal amplitude 20 1 mm In the patients with atrial fibrillation the mean values were 13 8 mm/s and 16 7 mm respectively

The difference between the mean value of the *descent rate* for the first 10 heart cycles and that of the following 10 cycles was calculated If possible continuous cycles were used for the measurement of the descent rate However, cycles in which the descent could not be clearly defined because of artifacts were excluded

Table 4 a) shows that the mean difference between the two decades of cycles was 0 28 mm/s in the whole material, it was 0.43 in the tracings with sinus rhythm and — 0 09 in those with atrial fibrillation In neither series was the difference between the two mean values statistically significant

The variance estimated by the formula shown in table 4 a) was 1 23 mm/s for the whole series, which means a coefficient of variation of about 8 % for the mean value of ten cycles in relation to that of the following ten it was of the same order in sinus rhythm as in atrial fibrillation

As the *maximal amplitude* seemed to show less variation than the descent rate this variable was measured during only 10 cycles The mean value of the first 5 cycles and the difference between this mean and that of the following 5 cycles were calculated

Table 4 a) shows that the difference between the means was 0 19 mm in the whole series 0 13 in sinus rhythm and 0 33 in atrial fibrillation The variance for the whole series was 0 48 mm which means a coefficient of variation of about 4 % for the mean value of five cycles in relation to that of the following five (about 2 % in sinus rhythm and 4 % in atrial fibrillation)

THE VARIATION DURING DISCONTINUOUS RECORDING

The figures for the *variance given* above cannot be considered as a true estimate of the error of the method since the pair of mean values were from the same recording

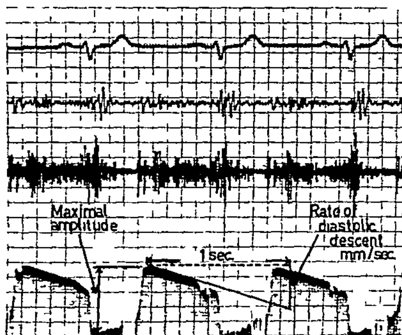

Fig 4 *UCG tracing from the anterior mitral leaflet in a patient with mitral stenosis Paper speed 50 mm/s*

by the test plug corresponded to 2 cm on the ECG paper This test was repeated at the end of each tracing

The paper speed of the Mingograph at all recordings was 50 mm/s

THE MEASUREMENT OF THE DIASTOLIC DESCENT-RATE AND THE MAXIMAL AMPLITUDE

Two variables were determined in every UCG tracing, the rate of diastolic descent (descent rate) and the maximal amplitude as shown by fig 4

The descent rate was measured in the following way a straight line was drawn with a pencil along the descent and lengthened suitably, a transparent set square was then placed over the tracing This square was graduated in millimeters along the vertical part and had a marking on the horisontal part 5 cm from the right angle The horisontal part was brought parallell to the baseline of the tracing and placed so that the line of descent intersected the 5 cm marking, as the paper speed was 50 mm/s the rate of descent could then be read at the point of intersection between the line of descent and the vertical graduated scale

The mean values of descent rate and maximal amplitude were determined in each tracing, 20 heart cycles being used for the former and 10 cycles for the latter calculation

Finally the above mentioned test belonging to the tracing studied was exactly measured, the mean values were corrected if the test diverged from the 2 cm value

AN EVALUATION OF THE ERRORS OF THE UCG-METHOD

The variation of the parameters measured in the ultrasound cardiogram has apparently not been studied in detail previously

Effert (33) considered that a range of more than 4° (about 4 mm s) of the

S nus rl ythm

Ca e	Heart rate	S te of recording Inter space	D tance from sternum (cm)	Descent rate (mm/s) Heart cycles 1—10	11—20	Maxi nal ampl tude (mm) Heart cycles 1—5	6—10
160930	50	4th	6 0	7 5	7 4	12 2	12 2
	0	5th	5 0	10 4	9 9	11 °	11 4
	50	3rd	7 5	6 4	7 9	13 6	12 8
	50	4th	6 0	5 4	7 5	12 4	11 8
	50	4th	4 5	6 7	8 0	11 8	11 8
2 0913	80	3rd	3 0	°6 0	25 9	21 8	21 6
	80	4th	4 0	°8 3	3° 0	21 8	22.2
	80	4th	2 0	24 0	25 3	22 6	°° 4
	80	5th	3 5	°3 1	21 6	21 8	°1 2
	80	4th	3 8	°8 0	28 0	21 6	21 0
101118	65	3rd	4 0	9 2	9 0	23 4	23 6
	6	4th	4 0	1° 1	11 2	22 2	21 8
	6	3rd	3 0	8 9	7 4	22 2	23 2
	6	3rd	3 5	10 8	9 4	23 4	23 6
300614	4	3rd	4 0	13 4	13 2	12 0	11 8
	4	4th	3 0	°0 4	15 6	12 0	11 8
	5	3rd	°0	16 1	15 3	13 4	14 4
	5	4th	3 5	14 7	15 3	13 8	13 8
210516	88	3 d	3 5	9 0	10 9	15 8	15 6
	88	4th	3 5	12 5	10 5	22 6	21 6
	88	4th	4 0	13	15 5	1 0	16 4
	88	3rd	° 5	11 9	10 4	21 4	°3 2
	88	3rd	4 0	14	13 6	23 4	23 8

A r al f br llat on

090103	8	3rd	2 0	1 0	17 6	18 0	17 6
	8	3rd	3 0	18 8	16 7	19 2	19 2
	87	3 d	4 5	19 8	19 7	18 6	17 8
	8	3rd	4 5	1 4	17 2	—	—
	8	4th	4 0	18 1	18 6	16 4	17 0
	8	3rd	4 0	18 3	18 1	°0 6	20 4
0 0710	84	3rd	3 5	13 1	13 7	20 2	18 2
	68	4th	3 0	°3 0	23 7	21 2	20 4
	°	3rd	4 0	1 9	20 9	19 0	20 0
		4th	5 0	18 9	°1 0	19 4	18 6

Table 4 *Mean values of descent rate and maximal amplitude (for 10 and 5 heart cycles respectively) during continuous recording*

Sinus rhythm

Case	Heart rate	Site of recording Inter space	Distance from sternum (cm)	Descent rate (mm/s) Heart cycles 1—10	11—20	Maximal amplitude (mm) Heart cycles 1—5	6—10
370331	75	3rd	2 5	10 6	10 7	20 0	20 2
	75	3rd	3 0	14 8	13 4	24 6	23 8
	60	3rd	3 0	16 1	14 8	24 8	24 6
	60	3rd	3 5	14 7	14 7	23 2	23 2
	60	3rd	3 0	15 5	18 4	24 8	24 4
	60	3rd	3 0	15 7	13 3	19 8	20 6
340213	79	3rd	3 5	13 6	14 8	18 8	18 6
	80	3rd	3 5	16 8	13 5	20 6	20 6
	80	3rd	4 2	14 0	12 2	20 2	20 2
	80	3rd	4 2	16 7	17 5	19 8	18 8
	80	3rd	3 0	15 3	12 4	20 0	18 4
	80	3rd	3 7	15 7	15 2	19 0	18 4
150111	67	3rd	3 5	13 7	12 0	27 4	28 2
	67	4th	3 0	16 4	16 3	19 8	20 8
	67	3rd	3 5	15 5	12 7	26 8	26 6
	62	3rd	3 5	11 3	12 6	24 0	21 8
150928	60	3rd	4 5	15 1	15 2	23 4	23 4
	60	4th	4 0	16 2	12 9	21 2	21 0
	68	4th	3 5	14 2	13 6	21 2	20 2
230627	77	3rd	4 5	7 1	6 9	19 6	17 0
	77	4th	4 5	9 6	9 0	14 8	14 4
	83	4th	5 0	8 3	6 4	11 2	10 6
090701	66	4th	4 5	17 5	16 6	22 2	21 2
	66	5th	4 5	16 8	19 1	20 6	20 4
	70	4th	3 5	17 5	16 9	22 4	22 2
	65	4th	3 5	21 7	20 4	22 2	20 6
111112	76	4th	3 5	14 9	13 3	22 0	22 0
	76	3rd	4 2	15 0	13 6	25 2	24 2
	85	4th	3 5	12 0	12 7	23 6	23 0
	85	4th	4 5	12 5	12 2	24 8	25 0
	75	4th	4 0	14 2	14 3	24 0	22 4
	75	5th	4 0	19 1	16 4	22 2	22 6
161012	73	4th	4 0	26 3	26 6	23 2	23 8
	70	4th	4 0	25 8	27 6	23 4	23 4
	65	4th	4 5	27 7	26 9	24 2	23 6

In a new series of 18 patients 9 with sinus rhythm and 9 with atrial fibrilla tion, two recordings were performed from the same site on the chest wall table 5 After the first recording the crystal was removed from the chest wall, at the second it was again placed at the same site and with the same inclination

The mean values of the descent rate and the maximal amplitude in the whole series were 20 1 *mm/s and* 17 8 *mm* (20 1 mm/s and 18 9 mm in sinus rhythm and 20 1 mm/s and 16 6 mm respectively in atrial fibrillation)

The descent rate of each recording was calculated as the mean value of 20 heart cycles the maximal amplitude as the mean of 10 cycles

The mean difference in *descent rate* between the first and the second recording in 46 examinations in patients with sinus rhythm and with atrial fibrillation was 0 05 mm/s, 0 42 in the former and — 0 17 in the latter patients, table 5 a) The difference between the two recordings was not statistically significant

The variance was 1 75 mm/s for the whole series (1 85 mm/s in sinus rhythm and 1 69 in atrial fibrillation)

The mean difference in *maximal amplitude* between the two recordings was 0 10 *mm in* 46 *examinations* (0 43 mm in sinus rhythm and — 0 12 in atrial fibrillation) The difference between the two recordings was not significant

The variance was 1 11 mm for the whole series (1 24 mm in sinus rhythm and 1 02 in atrial fibrillation)

The coefficients of variation for these duplicate recordings were about 7 % for the descent rate and about 6 % for the maximal amplitude

Table 5 *Duplicate recordings from the same site on the chest wall (recordings I and II)* (The descent rate was determined as the mean value of 20 heart cycles the maximal amplitude as the mean value of 10 cycles)

Sinus rhythm

Case	Heart rate	Site of recording: Inter space	Site of recording: Distance from sternum (cm)	Descent rate (mm/s) I	Descent rate (mm/s) II	Maximal amplitude (mm) I	Maximal amplitude (mm) II
301127	55	4th	4 0	19 5	17 1	21 6	21 0
	66	4th	4 0	15 6	15 5	16 7	16 1
	66	3rd	4 5	13 7	11 4	14 5	13 1
[illegible]61021	66	4th	4 0	29 1	28 1	21 3	20 7
	66	4th	4 0	[illegible]8 8	26 7	24 5	24 4
[illegible]0527	[illegible]8	3rd	4 0	[illegible]0 2	21 6	16 7	18 4
250909	2	4th	3 5	9 5	10 4	20 4	19 4
	72	5th	4 0	11 5	11 2	20 1	18 0
[illegible]40923	80	3rd	3 5	9 8	7 3	18 0	13 9
320508	64	3rd	4 0	22 5	20 3	21 4	19 8
	64	4th	4 0	24.7	23 6	19 2	20 5
140831	62	4th	3 5	18 7	20 2	22.4	22 5

(Table 4 continued)

Atrial fibrillation

Case	Heart rate	Site of recording: Inter space	Site of recording: Distance from sternum (cm)	Descent rate (mm/s) Heart cycles 1—10	Descent rate (mm/s) Heart cycles 11—20	Maximal amplitude (mm) Heart cycles 1—5	Maximal amplitude (mm) Heart cycles 6—10
230627	86	4th	3 5	8 5	7 5	12 8	13 0
	95	4th	3 5	9 0	8 0	11 2	11 2
	95	4th	4 5	8 2	7 2	10,8	10 4
110412	70	4th	4 5	17 2	18 8	17 4	16 6
	58	5th	4 0	14 1	14 2	16 6	17 6
220527	52	4th	4 5	11 7	12 3	14 6	14 0
	78	4th	4 0	10 3	9 0	20 6	20 4
	78	5th	3 5	12 2	11 5	18 4	18 8
	100	4th	4 0	10 2	10 5	22 2	22 4
	100	4th	4 5	9 1	10 2	21 8	22 0
	100	5th	4 0	13 1	12 0	17 4	17 0
220709	47	3rd	3 0	7 9	9 6	13 4	13 6
	47	4th	7 0	10 8	11 7	12 4	11 4
	37	3rd	4 0	11 0	8 7	16 4	15 4
	37	3rd	5 0	11 2	10 6	15 0	14 8

Table 4 a *Mean values of descent rate and maximal amplitude in the patients of table 4 Differences between mean values of heart cycles 1—10 and 11—20 (descent rate) and heart cycles 1—5 and 6—10 (maximal amplitude) Sinus rhythm (S R) and atrial fibrillation (A F)*

Rhythm	Descent rate (mm/s) Number of patients	Descent rate (mm/s) Mean value ± S E of mean value	Maximal amplitude (mm) Number of patients	Maximal amplitude (mm) Mean value ± S E of mean value
S R	13	15 09 ± 1 63	13	20 11 ± 1 16
A F	6	13 75 ± 1 86	6	16 67 ± 1 30
S R + A F	19	14 67 ± 1 24	19	19 02 ± 0 95

Rhythm	Number of diff	Differences between mean values of heart cycles 1—10 and 11—20: Mean diff ± S E of mean diff	Variance $\frac{\Sigma d^2}{2n}$	Number of diff	Differences between mean values of heart cycles 1—5 and 6—10: Mean diff ± S E of mean diff	Variance $\frac{\Sigma d^2}{2n}$
S R	58	0 43 ± 0 22	1 46	58	0 13 ± 0 13	0 46
A F	25	−0 09 ± 0 26	0 80	24	0 33 ± 0 21	0 54
S R + A F	83	0 28 ± 0 17	1 23	82	0 19 ± 0 11	0 48

Table 5 a *Mean values of descent rate and maximal amplitude in the patients of table 5 Differences between recording I and II Sinus rhythm (S R) and atrial fibrillation (A F)*

Rhythm	Descent rate (mm/s)			Maximal amplitude (mm)		
	Number of patients	Mean value ± S E. of mean value		Number of patients	Mean value ± S E. of mean value	
S R	9	20.11 ± 2.54		9	18.94 ± 0.81	
A F	9	20.07 ± 2.66		9	16.59 ± 1.60	
S R + A F	18	20.09 ± 1.79		18	17.77 ± 0.92	
	Number of diff	Differences between M_{20} of recording I and II		Number of diff	Differences between M_{10} of recording I and II	
		Mean diff ± S E. of mean diff	Variance $\frac{\Sigma d^2}{2n}$		Mean diff ± S E. of mean diff	Variance $\frac{\Sigma d^2}{2n}$
S R	17	0.42 ± 0.47	1.85	17	0.43 ± 0.38	1.24
A F	29	0.17 ± 0.35	1.69	26	−0.12 ± 0.27	1.02
S R + A F	46	0.05 ± 0.27	1.75	43	0.10 ± 0.23	1.11

THE VARIATIONS OF RECORDINGS FROM DIFFERENT SITES ON THE CHEST WALL

The variation of the two variables when UCG tracings were recorded from different sites on the chest wall in the same patient was studied in a series of 10 consecutive patients 3 with sinus rhythm and 7 with atrial fibrillation table 6

Recordings from two sites (A and B in table 6) were made at the same examination in all patients At each site duplicate recordings (I and II in table 6) were made the crystal was removed from the chest wall between them as described above

The descent rate was calculated as the mean value of 20 heart cycles the maximal amplitude as the mean of 10 cycles

The differences were calculated between the values obtained for descent rate and maximal amplitude of recording I and II from the same site and between the corresponding values from the different sites A and B

Table 6 a shows that the mean difference between the values of descent rate and maximal amplitude from 20 recordings I and II was 0.44 mm/s and 0.30 mm respectively Neither of these differences was statistically significant

The corresponding differences between recordings from the different sites A and B were − 2.77 mm/s and 0.61 mm respectively The former difference was significant ($p < 0.01$) while the latter was not

The influence of the site of recording in relation to the error of the method when two tracings were performed at the same site was studied by analysis of variance Table 6 a) shows that the variance of the differences between descent rates obtained from UCG-tracings recorded from different sites was 14.03 The variance of the differences between recordings from the same site was 2.40 The corresponding variances

(Table 5 continued)

Case	Heart rate	Site of recording: Inter space	Site of recording: Distance from sternum (cm)	Descent rate (mm/s) I	Descent rate (mm/s) II	Maximal amplitude (mm) I	Maximal amplitude (mm) II
111124	58	4th	2.5	25.0	23.6	17.9	16.7
081008	80	3rd	3.5	28.5	32.6	17.8	18.1
	73	3rd	3.5	32.0	31.8	18.0	20.2
	80	3rd	4.5	30.6	32.0	15.8	17.3
	80	4th	4.0	33.8	30.9	16.8	15.7
Atrial fibrillation							
030521	72	4th	4.0	16.7	16.5	11.6	12.8
	72	5th	4.0	19.6	19.0	12.5	11.1
080529	70	3rd	5.5	19.7	22.0	13.6	17.4
	70	4th	5.0	22.9	24.7	13.5	15.1
	70	4th	6.5	24.2	28.0	16.3	16.3
090102	72	3rd	3.5	21.8	22.1	9.7	9.1
	72	4th	4.0	26.4	22.5	9.9	9.1
	73	4th	4.0	21.3	19.1	10.2	9.7
080823	68	3rd	3.0	28.6	29.1	17.3	16.1
070127	50	3rd	4.0	14.2	9.8	—	—
	50	3rd	6.0	9.0	9.7	—	—
	50	4th	4.0	12.7	11.9	14.7	14.9
	50	4th	6.5	9.9	9.6	13.5	14.0
	54	4th	5.0	10.6	10.4	13.7	13.5
150502	60	3rd	3.0	32.0	32.7	17.8	18.3
	60	4th	3.5	31.3	31.2	18.8	18.8
	60	4th	5.0	32.2	31.5	16.9	19.9
	60	5th	3.0	34.0	36.6	16.8	19.1
161003	52	4th	5.0	9.9	8.8	29.7	28.0
	52	4th	6.0	9.6	10.8	26.0	26.2
	52	5th	6.0	9.4	11.6	24.6	23.5
090816	76	3rd	3.5	22.6	23.9	17.5	19.2
	76	3rd	5.0	19.2	21.5	20.0	18.2
	76	4th	3.0	24.1	22.9	18.4	
	76	4th	5.0	20.9	23.5	13.7	14.3
120113	42	3rd	4.0	10.6	10.7	18.4	17.1
	42	3rd	5.0	12.3	11.8	21.2	20.0
	42	4th	3.5	12.5	11.3	17.1	17.7
	44	4th	5.0	14.8	14.5	23.2	22.1

Table 6 a *Mean values of descent rate and maximal amplitude in the patients of table 5. Differences between recording I and II. Sinus rhythm (S R) and atrial fibrillation (A F)*

Rhythm	Descent rate (mm/s)		Maximal amplitude (mm)	
	Number of patients	Mean value ± S E. of mean value	Number of patients	Mean value ± S E. of mean value
S R	9	20 11 ± 2 54	9	18 94 ± 0 81
A F	9	20 07 ± 2 66	9	16 59 ± 1 60
S R + A F	18	20 09 ± 1 79	18	17 77 ± 0 92

Rhythm	Number of diff	Differences between M_{20} of recording I and II: Mean diff ± S E. of mean diff	Variance $\frac{\Sigma d^2}{2n}$	Number of diff	Differences between M_{10} of recording I and II: Mean diff ± S E. of mean diff	Variance $\frac{\Sigma d^2}{2n}$
S R	17	0 42 ± 0 47	1 85	17	0 43 ± 0 38	1 24
A F	29	−0 17 ± 0 35	1 69	26	−0 12 ± 0 27	1 02
S R + A F	46	0 05 ± 0 27	1 75	43	0 10 ± 0 23	1 11

THE VARIATIONS OF RECORDINGS FROM DIFFERENT SITES ON THE CHEST WALL

The variation of the two variables when UCG tracings were recorded from different sites on the chest wall in the same patient was studied in a series of 10 consecutive patients 3 with sinus rhythm and 7 with atrial fibrillation table 6

Recordings from two sites ('A and B in table 6) were made at the same examination in all patients At each site duplicate recordings (I and II in table 6) were made the crystal was removed from the chest wall between them as described above

The descent rate was calculated as the mean value of 20 heart cycles the maximal amplitude as the mean of 10 cycles

The differences were calculated between the values obtained for descent rate and maximal amplitude of recording I and II from the same site and between the corresponding values from the different sites A and B

Table 6 a shows that the mean difference between the values of descent rate and maximal amplitude from 20 recordings I and II was 0 44 mm/s and 0 30 mm respectively Neither of these differences was statistically significant

The corresponding differences between recordings from the different sites A and B were − 2 77 mm/s and 0 61 mm respectively The former difference was significant ($p<0.01$) while the latter was not

The influence of the site of recording in relation to the error of the method when two tracings were performed at the same site was studied by analysis of variance Table 6 a) shows that the variance of the differences between descent rates obtained from UCG-tracings recorded from different sites was 14 03 The variance of the differences between recordings from the same site was 2 46 The corresponding variances

Table 6 *Duplicate recordings (I and II) from two different sites (A and B) on the chest wall*

Case	Heart rate	Site of recording A: Inter space	Site of recording A: Distance from sternum (cm)	Descent rate (mm/s) I	Descent rate (mm/s) II	Maximal amplitude (mm) I	Maximal amplitude (mm) II	Site of recording B: Inter space	Site of recording B: Distance from sternum (cm)	Descent rate (mm/s) I	Descent rate (mm/s) II	Maximal amplitude (mm) I	Maximal amplitude (mm) II
070107	80	3rd	4 0	10 0	8 1	10 8	8 4	4th	4 5	15 0	14 8	12 5	13 2
170418	70	3rd	4 0	21 5	16 9	14 3	12 0	4th	4 0	26 0	24 6	15 8	14 0
141105	74	3rd	4 5	14 2	16 9	22 5	24 0	4th	4 0	23 4	19 1	22 1	21 6
100918	90	3rd	4 5	35 5	36 1	16 3	15 1	4th	4 0	35 7	34 8	15 5	16 5
110419	46	3rd	3 5	13 7	13 9	20 0	19 6	4th	3 5	16 6	15 6	16 3	18 7
140531	84	4th	3 0	13 6	14 9	14 0	13 4	4th	5 0	13 6	12 9	15 2	16 4
141130	54	3rd	3 5	21 7	18 3	18 9	19 1	4th	3 5	18 9	20 8	13 5	14 2
080410	88	4th	2 5	31 9	32 7	21 7	21 4	4th	4 0	33 9	36 9	21 9	21 4
33062[illegible]	74	3rd	3 [illegible]	17 7	14 9	19 5	20 6	4th	3 5	19 3	20 1	15 9	15 0
080816	50	4th	4 0	10 3	12 9	18 6	15 0	4th	3 0	15 2	13 7	16 8	16 5

Table 6 a. *Mean values of descent rate and maximal amplitude in the patients of table 6 Differences between duplicate recordings from the same site and between recordings from different sites on the chest wall*

	n	Descent rate (mm/s)	Maximal amplitude (mm)
Mean values of patients (± S.E. of mean)	10	20.17 ± 2.63	16.96 ± 1.08
Differences between duplicate recordings I and II (Mean diff ± S.E. of mean diff.)	20	0.44 ± 0.50	0.30 ± 0.33
Differences between recordings from site A and B (Mean diff ± S.E. of mean diff.)	10	−2.77 ± 0.84	0.61 ± 0.88

Analysis of variance

	Degrees of freedom	Variances: Descent rate (mm/s)	Variances: Maximal amplitude (mm)
Between recordings from site A and B	10	14.03	7.31
Between recording I and II from sites A and B	20	2.46	1.09

F test $F_{10,20}$ (descent rate) $= 5.69$ ($p < 0.001$)
$F_{10,20}$ (maximal amplitude) $= 6.71$ ($p < 0.001$)

for the maximal amplitude were 7.31 and 1.09. When the variances were tested by the F test a highly significant influence of the site of recording was found both upon the descent rate and the maximal amplitude (table 6 a).

(In the patients of table 6 two recordings were also performed from the same site on two *different days*. The variance of the differences between these recordings was of the same order as that for the differences between the duplicate recordings I and II at the same examination.)

The difference in descent rate between recordings from site A and site B was significant: higher values were obtained from the latter site in seven patients. The recordings from site A originated in seven patients from the third interspace and in three patients from the fourth. All recordings of site B originated from the fourth interspace.

Even if the material was too small to allow any definite conclusions this observation indicated that higher values of descent rate are to be expected if UCG tracings are recorded from the fourth interspace.

The series of 71 patients of the present study was used in order to get a larger material for the comparison of descent rates and maximal amplitudes in tracings from the two interspaces. In 46 of these patients, 24 with sinus rhythm and 22 with atrial fibrillation, UCG-tracings were recorded both from the third and fourth interspaces.

At first the mean values were calculated for the descent rate and the maximal amplitude of all tracings recorded from the third respectively the fourth interspace in every patient; then the differences between the means of the interspaces were calculated.

Table 7 illustrates that the mean value of descent rate in recordings *from* the fourth interspace was significantly higher both in patients *with* sinus rhythm and with atrial fibrillation. In twelve patients the difference was 3

Table 7 *Recordings from the 3rd and 4th costal interspaces in 24 patients with sinus rhythm patients with atrial fibrillation*

	n	Descent rate (mm/s) 3rd interspace	Descent rate (mm/s) 4th interspace	Maximal amplitude (3rd interspace	Maximal amplitude (4th inte
Sinus rhythm					
Mean value ± S E of mean	24	14 71 ± 1 33	17 23 ± 1 16	20 05 ± 0 77	19 94 ±
Mean difference between 3rd and 4th interspace ± S E of mean difference		— 2 52 ± 0 53 ($p < 0\ 001$)		0 11 ± 0 41 ($p > 0\ 1$)	
Atrial fibrillation					
Mean value ± S E of mean	22	14 04 ± 0 80	15 48 ± 0 71	19 88 ± 0 87	19 24 ±
Mean difference between 3rd and 4th interspace ± S E of mean difference		— 1 44 ± 0 25 ($p < 0\ 001$)		0 64 ± 0 69 ($p > 0\ 1$)	

mm/s or more, in five of those it was more than 5 mm/s, the greatest difference was 9 mm/s

Table 7 also shows that the difference in maximal amplitude between the two interspaces was not significant

THE RELATION BETWEEN THE DURATION OF THE HEART CYCLE AND THE DIASTOLIC DESCENT-RATE IN ATRIAL FIBRILLATION

In 9 patients with atrial fibrillation the relation between the duration of the heart cycle and the descent rate was studied

The descent-rate was plotted against the R—R interval, both against that during which the descent occurred and against the preceding one, in separate diagrams The values from about one hundred cycles were used in every patient

The descent-rate seemed to be independent of the length of the heart cycle since no correlation was found in any patient between the descent rate

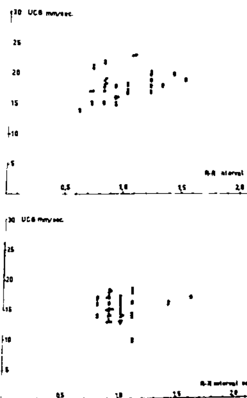

Fig 5 *The diastolic descent rate of the LC tracing related to the R—R interval (during which the descent occurred) in two patients with atr fibrillation*

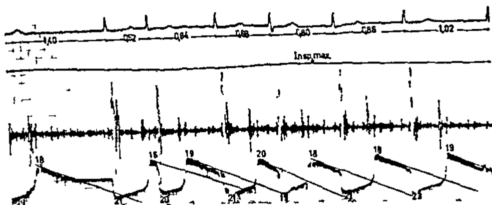

Fig 6 R—R interval in relation to diastolic descent rate (measuring values indicated at the top of the UCG-tracing) and to maximal amplitude (indicated at the bottom of the tracing) in a patient with atrial fibrillation

and the preceding or actual R—R interval

The plotting diagram of two cases are illustrated in fig 5 Fig 6 shows the UCG tracing from a patient with a wide range of duration of the R—R intervals the descent rate and the maximal amplitude showed but small variations

THE VARIATION OF THE UCG FINDINGS WITH DIFFERENT HEART RATES IN PATIENTS WITH SINUS RHYTHM

In sinus rhythm the UCG-findings in heart cycles of different duration were studied by the recording of tracings at rest and during exercise in the supine position in 9 patients

The descent rate and the maximal amplitude were calculated as the mean of 10 heart cycles

After the recording at rest the crystal was retained in the same position while the patient began pedalling a bicycle ergometer the recording was continued during the exercise The work load was increased until the highest heart rate was reached at which it was still possible to measure the descent rate with any reliability which occurred at a load varying between 100 and 300 kpm/min (In case 02 03 08 of table 8 the exercise was interrupted because of respiratory distress)

Table 8 and fig 7 illustrates that in some patients the descent rate could still be satisfactorily identified at heart rates of more than 100 beats per min the limiting factor most often was an interference with the peak of the tracing caused by the atrial systole

In the first four patients of table 8 the rate of descent and the maximal amplitude were determined at two different heart rates during exercise

The mean difference in heart rate between the rest and highest exercise values was 30 beats/min range 10—43 In seven patients the descent rate was higher during exercise range 0 1—3 8 mm/s in two it was higher at rest, range 0 7—7 0 mm/s

The maximal amplitude was larger during exercise in five patients range 0 2—3 0 mm in three patients the rest values were larger range 0 1—1 1 mm

Thus the difference between rest and exercise values for both the variables were small and the mean differences were not significant

Table 8 *Recordings performed at rest and during exercise in 9 patients with sinus rhythm*

Case	Heart rate	Descent rate (mm/s)	Maximal amplitude (mm)
210509	R 65	20 6	19 4
	E 80	22 1	18 7
	E 98	21 4	18 6
330625	R 63	20 8	20 2
	E 86	20 9	20 6
	E 103	18 8	20 4
260501	R 54	21 9	24 9
	E 74	21 2	24 4
	E 85	18 8	25 1
291013	R 63	21 3	16 4
	E 100	24 0	17 0
	E 120	20 4	20 0
170412	R 73	24 2	25 5
	E 100	26 9	26 5
020308	R 66	11 4	21 2
	E 76	13 5	20 1
180610	R 83	24 2	18 7
	E 103	18 2	19 7
320606	R 80	15 0	12 1
	E 110	15 4	12 1
201013	R 64	27 5	18 2
	E 86	31 3	17 1

	n	Descent rate (mm/s)	Maximal amplitude (mm)
Mean value at rest ± S E of mean	9	20 77 ± 2 66	21 50 ± 3 40
Mean value at exercise ± S E of mean	9	19 62 ± 1 37	19 58 ± 1 40
Mean difference between rest and exercise values ± S F of mean diff	9	— 0 73 ± 0 97	— 0 04 ± 0 28

THE UCG FINDINGS IN SINUS RHYTHM AND IN ATRIAL FIBRILLATION IN THE SAME PATIENT

UCG-tracings were recorded both during atrial fibrillation and with sinus rhythm in 11 patients (table 9) The tracings were obtained from the same site of recording at the two examinations The mean interval between them was 6 days, range 1—18 days

The first two patients of table 9 were examined the first time during sinus rhythm and the second after atrial fibrillation had occurred The other nine patients were examined the first time when in atrial fibrillation, the second examination was performed after cardioversion with electric countershock

The descent rate was calculated as the mean of 20 heart cycles the maximal amplitude as the mean of 10 cycles

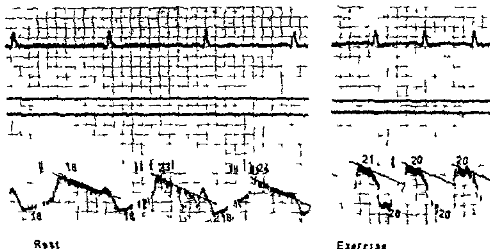

Fig 7 UCG tracings recorded at rest (heart rate 60 beats/min) and during exercise (heart rate 120 beats/min) in a patient with sinus rhythm

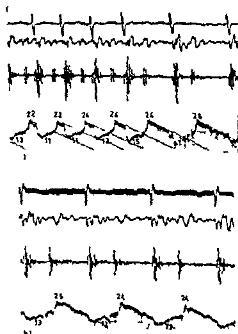

Fig 8 UCG-tracings recorded a) during atrial fibrillation (heart rate 120 beats min) and b) during sinus rhythm (heart rate 60 beats min) in a patient operated upon for mitral stenosis

The descent rate was higher in sinus rhythm in 15 of 24 recordings in 8 of these the difference was more than 3 mm/s the greatest difference was 7 3 mm/s However the mean difference between atrial fibrillation and sinus rhythm was not statistically significant

The maximal amplitude in 17 recordings was larger in sinus rhythm than in atrial fibrillation in 6 of these the difference was more than 3 mm the greatest difference was 5 4 mm The mean difference between atrial fibrillation and sinus rhythm was probably significant

Fig 8 shows UCG tracings from one patient in atrial fibrillation and in sinus rhythm In spite of the different rhythms and a difference in heart rate of 60 beats/min the rate of descent and maximal amplitude were of the same order

THE INFLUENCE OF THE RESPIRATION ON THE UCG TRACING

All UCG tracings of the present investigation were recorded during normal breathing

Table 9 *Recordings performed during atrial fibrillation (A F) and during sinus rhythm (S R) 11 patients*

Case	Heart rate A F	Heart rate S R	Site of recording: Inter-space	Site of recording: Distance from sternum (cm)	Descent rate (mm/s) A F	Descent rate (mm/s) S R	Maximal amplitude (mm) A F	Maximal amplitude (mm) S R
230627	95	77	4th	4.5	7.8	9.0	10.6	14.6
100211	75	68	4th	3.5	9.9	14.0	8.5	9.8
	75	68	5th	4.0	10.9	15.0	8.9	14.3
	75	68	5th	4.5	10.6	15.2	8.9	11.0
201013	72	73	4th	3.5	26.3	19.9	16.3	14.7
	72	73	4th	5.5	21.4	22.4	14.3	12.9
260323	67	70	3rd	3.5	46.5	42.5	20.9	22.4
	67	70	3rd	6.0	35.9	38.8	19.6	21.1
	67	70	4th	4.5	30.4	37.3	18.6	21.8
160930	129	62	3rd	3.5	22.2	26.3	12.5	16.4
	129	62	4th	5.0	24.3	23.7	13.4	11.7
200210	97	97	3rd	3.0	28.5	30.1	18.6	21.6
	97	97	4th	3.0	28.5	31.5	16.2	21.2
	97	97	4th	5.0	33.2	29.5	19.3	19.6
081123	72	72	4th	4.5	30.3	33.5	20.5	20.9
200826	83	88	4th	3.0	36.8	34.0	18.1	21.5
110621	73	84	4th	3.0	18.2	17.4	19.6	18.9
	73	84	4th	5.0	16.9	16.9	16.8	17.7
	73	84	4th	6.5	16.3	13.7	16.0	17.3
221223	71	90	3rd	4.5	23.6	25.5	22.1	24.9
	71	90	4th	3.0	25.6	24.0	21.9	19.1
200614	59	52	3rd	3.5	27.9	33.5	23.2	22.0
	59	52	4th	4.0	34.9	35.0	24.8	20.8
	59	52	4th	5.5	32.8	40.1	23.5	23.0

	n	Descent rate (mm/s)	Maximal amplitude (mm)
Mean value of patients ± S E of mean	11	25.36 ± 2.95	17.64 ± 1.28
Differences between recordings during A F and S R (mean diff ± S E of mean diff)	24	− 1.21 ± 0.73 ($p > 0.1$)	− 1.14 ± 0.50 ($p < 0.05$)

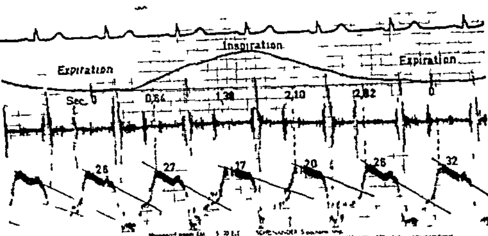

Fig 9 *UCG-tracing from a patient showing great variation in the diastolic descent rate during different phases of the respiration*

In 14 patients with mitral stenosis, 8 with sinus rhythm and 6 with atrial fibrillation the influence of the respiratory movements upon the UCG tracing was studied

A belt was placed around the chest of the patient for the recording of the respiratory movements The ends of the belt were connected by a rubber tubing containing an electrolyte which constituted one part of an electric resistance bridge the voltage fluctuations arising through the variations in resistance caused by the varying degree of stretching of the tubing were recorded by the Mingograph

The duration from the start of the respiratory cycle (deepest point of expiration) to the beginning of each diastolic descent was measured (fig 9) then the values obtained, that is time in seconds and rate of descent in mm/s were plotted against each other in a diagram (fig 10) Twenty respiratory cycles at least were studied in each patient

The mean time of the inspiratory end position indicated in the plotting diagram (fig 10) was calculated as the mean of all the cycles studied The mean values of the descent rates during the first and last second of the respiratory cycle and of those within one second around the "mean inspiratory end position" were calculated

Table 10 shows the mean values and ranges for these periods In 10 of the 14 patients studied the lowest mean value was found in the period around the inspiratory end position The plotting diagram in one of these patients is illustrated in fig 10

Fig 9 shows the UCG tracing from another patient in which the descent rate showed a great variation during the different phases of respiration

DISCUSSION

The number of heart cycles which should be measured to determine the rate of diastolic descent and the maximal amplitude of each UCG tracing is the first problem to be discussed on the basis of the methodological studies

Effert (33) used the average value of measurements during 5 to 10 cycles to determine the descent rate Edler (26) calculated the average value of the same

Table 10 *Mean value and range of descent rate during different periods of the respiratory cycle in 8 patients with sinus rhythm (S R) and 6 patients with atrial fibrillation (A I)*

Case	Rhythm	Site of recording: Inter space	Site of recording: Distance from sternum (cm)	First second: n	First second: m	First second: range	Inspiratory end position (mean ± ½ sec): n	Inspiratory end position (mean ± ½ sec): m	Inspiratory end position (mean ± ½ sec): range	Last second: n	Last second: m	Last second: range
301127	SR	4th	4 0	10	19 7	23—18	11	15 2	17—12	9	16 7	21—14
240923	SR	3rd	3 0	27	11 0	17— 6	23	8 7	15— 8	19	9 8	16— 7
310814	SR	4th	3 5	21	20 5	25—17	21	16 2	24—13	10	18 9	26—18
261107	SR	4th	3 0	30	20 3	26—16	25	16 9	18—12	15	22 8	26—18
120830	SR	4th	4 5	21	25 5	32—15	30	22 7	29—18	17	27 1	32—21
2 0909	SR	4th	4 0	23	13 4	18— 9	19	11 6	15— 8	18	13 4	17—10
270909	SR	3rd	3 0	31	25 1	30—20	28	24 3	29—20	20	25 8	29—21
330315	SR	5th	5 0	17	14 8	18—14	29	16 7	20—13	7	15 9	18—14
030 21	AI	4th	3 0	19	16 0	19—13	20	15 4	20—15	8	16 4	19—13
260323	AI	3rd	3 5	20	18 0	27—15	16	18 1	21—15	16	17 9	20—15
070810	AI	4th	3 0	23	17 5	23—13	21	15 7	20—15	20	17 8	22—15
200826	AI	3rd	4 0	16	21 4	26—17	19	18 3	23—15	8	22 8	27—18
071003	AI	3rd	3 5	19	18 0	26—13	23	19 6	23—12	23	17 2	18—14
030 20	AI	3rd	3 [illegible]	31	27 [illegible]	32—22	29	22 9	28—17	27	21 8	27—17

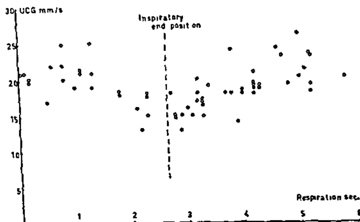

Fig 10 The diastolic descent rate plotted against the time in the respiratory cycle at which the descents started in a patient showing great variation in the rate of descent The time of the inspiratory end position was calculated as the mean of 20 respiratory cycles

variable from 20 or more cardiac cycles in each patient The number of heart cycles measured has not been commented upon in other reports of ultrasound cardiography in mitral valvular disease

In the present series a variance of 1.23 mm/s was found during continuous recording for the mean value of descent rate obtained from 10 heart cycles in relation to that obtained from the following 10 cycles In duplicate recordings from the same site on the chest wall a variance of 2.46 mm/s was found for the mean value of this variable calculated from 20 heart cycles

The expected variance for the descent rate as a mean value of measurements during 10 heart cycles can be estimated by the following calculations (taking into consideration the fact that the mean values of the pair of 10 cycles during continuous recording were correlated)

$E(S^2) = (1 - r) \times \text{var } M_{10}$ and

$E \text{ var } M_{20} = \frac{1}{2}(1 + r) \times \text{var } M_{10}$

which gives

$$\text{Var } M_{10} \simeq \frac{2 \times 2.46 + 1.23}{2} = 3.08$$

Thus $S(M_{10}) = 1.76$ mm/s and $S(M_{20}) = 1.57$ mm/s

If the same calculations are applied to the maximal amplitude the following estimate of the variance is found

$$\text{Var } M_5 \simeq \frac{2 \times 1.09 + 0.48}{2} = 1.33$$

which gives

$S(M_5) = 1.15$ mm and

$S(M_{10}) = 1.04$ mm

From these estimates of the variances for descent rate and maximal amplitude it is evident that the accuracy is not much increased if the descent rate is calculated from 20 instead of 10 heart cycles and the maximal amplitude from 10 instead of 5 cycles

The most important source of variation of these two variables in the UCG within the same patient is not "the error of the method" estimated as the variation during continuous recording or as the reproducibility of duplicate recordings from the same site on the chest wall Tables 6 and 7 show that the

Table 10 Mean values and range of Iscent rate during different periods of the respiratory cycle in 8 patients with sinus rhythm (SR) and 6 patients with atrial fibrillation (AF)

Case	Rhythm	Site of recording: Inter space	Distance from sternum (cm)	First second n	m	range	Inspiratory end position (mean ± ½ sec) n	m	range	Last second n	m	range
301127	SR	4th	4 0	10	19 7	23—18	11	15 2	17—12	9	16 7	21—14
240923	SR	3rd	3 0	27	11 0	17— 6	23	8 7	15— 8	19	9 8	16— 7
310814	SR	4th	3 5	21	20 5	25—17	21	16 2	24—13	10	18 9	26—18
261107	SR	4th	3 0	30	20 3	26—16	25	16 9	18—12	15	22 8	26—18
120830	SR	4th	4 5	21	25 5	32—15	30	22 7	29—18	17	27 1	32—21
250909	SR	4th	4 0	23	13 4	18— 9	19	11 6	15— 8	18	13 4	17—10
270909	SR	3rd	3 0	31	25 1	30—20	28	24 3	29—20	20	25 8	29—21
33031	SR	5th	5 0	17	14 8	18—14	29	16 7	20—13	7	15 9	18—14
030 [illegible]1	AF	4th	3 0	1[illegible]	16 0	19 13	2[illegible]	15 4	20—15	8	1[illegible] 1	19—13
[illegible]323	AF	3rd	3	20	18 0	27—15	1[illegible]	18 1	21—15	1[illegible]	17 9	20—15
070310	AF	4th	3 0	23	17 5	23—13	21	15 7	20—15	20	17 8	22—15
20 8[illegible]	AF	3rd	4 0	1[illegible]	21 4	2[illegible]—17	19	18 3	23—15	8	22 8	27—18
071[illegible]03	AF	3rd	3	1[illegible]	18 0	26 13	23	19 [illegible]	23—12	23	17 2	18—14
[illegible]	AF	3rd	3	31	27 5	32—22	29	22 9	28—17	27	21 8	27—17

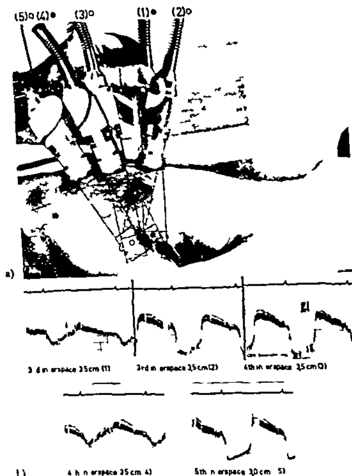

Fig 11 *UCG-trac ngs re orded from d fferent s tes on the chest wall in a pat ent w th m t al stenos s Fig 11 a) llus rates the pos t ons of the crystal at the record ng of the tra ngs in f g 11 b)*

The pos tion of the cry tal at each record ng was photographed by two cameras one placed behind the head of the patient taking p ctures of the crystal s ncl nation aga nst the sagittal plane of the che t another placed about 2 m eters from the s de of the pat ent took p ctures of the pos t ons of the crystal a d its incl nat on aga n t he hor zo tal plane The photos taken by the latter camera during f e record ngs were put together to one p cture wh ch was photographed f g 9 a)

The UCG-trac ngs were s multaneously registered by the pho ographic and the direct record ng methods With the photographic method the distance could be measured between the che t wall and the echo-giving structure (the anterior leaflet) Before these distances were tran ferred to the p cture a correction was made for the crystal s inclination against the sag ttal plane —The po tions of the leaflet when t was neare t the chest wall and most remote from t are ndicated by the hort lines perpend cular to the ultrasound beams, the distance between two such l nes represents the maximal amplitude of the tracing —The ultrasound beams emanat ing from the crystals marked with filled circles were d rected against one po nt of the leaflet the beams from those marked w th open circles were directed against another po nt.

variation is more dependent on the site of the chest wall from which the recording is performed

Fig 11 illustrates how the UCG tracing of the anterior mitral leaflet varies when the recording is performed from different sites on the chest wall with varying inclination of the crystal In recordings 1 and 4 the ultrasound beam was directed against the same point, the tracings from these recordings showed lower maximal amplitudes and slower descent rates than in those from the other recordings The descent-rates and maximal amplitudes of the recordings 2, 3 and 5 were more closely correlated to the surgeon's estimate of the mitral valve area and to the mobility of the anterior leaflet

The tracings from recordings 1 and 4 presumably reflected the motion pattern of the most basal and medial part of the anterior leaflet which evidently was not representative for the main part of the leaflet

The different inclinations of the crystal against the chest wall shown in fig 11 also explains why it is possible to record UCG tracings of the movements of the anterior mitral leaflet from such different sites of recording as the 3rd and 5th interspaces The greatest distance between the central parts of the ultrasound beams was about 30 mm at the level where the echoes were obtained, this distance corresponds well to the length of the anterior leaflet

Thus the site on the chest wall from which the UCG recording is performed is of importance for the result in some patients, especially for determination of the descent rate which in the present investigation showed significantly higher values in recordings from the 4th interspace

EFFERT (33) recorded the UCG tracings from the 3rd interspace generally 2—3 cm to the left of the midsternal line He found that tracings could also be recorded from the fourth interspace in patients with a very dilated left atrium, these were however considered as "abortive Kurven" with generally lower amplitude than in those recorded from the 3rd interspace This statement is not consistent with the present study in which the maximal amplitude was not significantly lower in the tracings recorded from the 4th interspace Nor was the possibility of recording UCG-tracings from the 4th interspace limited to patients with a very enlarged atrium in the present series the mean heart volume in 27 patients with sinus rhythm, in which UCG tracings were obtained from the fourth interspace, was 530 ml/m² BSA (range 415—715 ml/m²) In this respect the position of the heart within the chest and the anatomical configuration of the latter probably is of more importance than the size of the left atrium

The difference between UCG tracings recorded from various sites on the chest wall has also been commented upon by EFFERT et al (34), these authors emphasize that "in single post operative cases one can get various curves by recording in different positions of the transducers on the chest wall Therefore, the registration has to be achieved with special care, in order to avoid errors"

No close examination of the difference between curves from various sites of recording has, however, been published before

In the present series where UCG-findings were correlated to other variables, recordings were performed at different distances from the sternum within both the 3rd and 4th interspace whenever possible The mean values of descent rate and maximal amplitude within the respective interspaces were calculated the largest mean value was used for the correlations

The descent rate was not correlated to the length of diastole in patients with

studied the influence of different sites of recording the heart rate the heart rhythm and the respiration upon these variables were also examined

During continuous recording the coefficients of variation was 8 % for the mean value of the descent rate during 10 heart cycles in relation to that of the following 10, it was 4 % for the maximal amplitude when this variable was determined as the mean value of 5 heart cycles

In duplicate recordings the coefficients of variation were 7 % for descent rate and 6 % for maximal amplitude

The variances of the descent rate determined as the mean value of measurements during 10 and during 20 heart cycles were compared as well as those of maximal amplitude determined as the mean value of 10 and 5 heart cycles respectively Measurements of descent rate during 10 and of maximal amplitude during 5 cycles were found to be sufficient for determination of the two variables in each UCG tracing

The most important cause for the variation of the two parameters in the same patient was the site on the chest wall from which the recording was performed This was shown by analysis of variance applied to duplicate recordings from two different sites on the chest wall

In a series of patients the mean values of the two variables in recordings from the 3rd and 4th interspace were compared The descent rate was significantly higher in recordings from the fourth interspace while the difference in maximal amplitude was not significant between the two interspaces

The descent rate showed no correlation to the length of the heart cycle in atrial fibrillation Nor was this variable significantly influenced by the heart rate in sinus rhythm

In 11 patients the descent rate and the maximal amplitude were determined during atrial fibrillation and during sinus rhythm Only the maximal amplitude showed a probably significant difference between the two rhythms the mean value was slightly higher during sinus rhythm

When the effect of respiration upon the descent rate was studied in 14 patients a tendency towards lower rates was found at the inspiratory end position

atrial fibrillation This observation is consistent with the findings of EFFERT (33) but in contrast to those of GASSLER and SAMLERT (48) As EFFERT emphasizes the latter authors seemed to have correlated the length of diastole to the vertical distance between the highest point of the curve at the beginning of diastole and the point it had reached before the next systole irrespective of whether the curve had attained a horisontal level or not This proceeding must result in a certain correlation between the two variables in patients with low heart rates, a correlation which is not, however, of any interest if the descent rate is determined as in the present series

Nor did the descent rate and the maximal amplitude show any relation to the heart rate in patients with sinus rhythm This is of advantage when the degree of mitral stenosis is estimated by UCG since patients with sinus rhythm often have a fast heart rate resistant to medical treatment

The rhythm per se did not significantly influence the descent rate which was shown by comparing recordings obtained during sinus rhythm and in atrial fibrillation in the same patient This finding indicates the possibility of evaluating the degree of mitral stenosis independently of the heart rhythm which would be of value if atrial fibrillation supervenes when patients are observed for a longer time with repeated UCG-examinations, e g to detect restenosis after commissurotomy

The weaker correlation which was found in the present series between UCG findings and other variables in patients with atrial fibrillation could therefore hardly be explained by the effect of atrial fibrillation per se on the UCG tracing

EFFERT (33) emphasized that the patient must hold his breath while the UCG recording is performed to avoid influence of movements of the chest wall on the UCG tracing, the type of apnea (inspiratory or expiratory) was not mentioned, however

In the present investigation the patients breathed normally during the recording, this technique has always been used in this clinic The only disadvantage seen has been that in some patients the echo disappears at the inspiratory end position

The recording during apnea would have certain disadvantages, the patient can make a Valsalva or Muller manœuvre while holding his breath which would possibly influence the movement pattern of the mitral leaflets The reproducibility of the recording would also be influenced because it can be difficult to reproduce the same respiratory position from one examination to another Apnea with the chest wall in different positions would have the same effect as altering the position of the crystal on the chest wall

In the present study the descent rate was found to be lower during the period at the inspiratory end position in some patients No statistical evaluation was made of the differences between the mean values obtained during the various periods of respiration since the respiratory cycles were not of the same duration in the individual patient

The effect of inspiration would be the same as recording from different sites on the chest wall the ultrasound beam being directed against a more basal part of the leaflet during the inspiratory movement of the chest wall Whatever the cause of this variation it seemed to be of slight importance it is included in the variation found when the reproducibility of the method was studied

SUMMARY

The reproducibility of two variables determined in the UCG, the descent rate and the maximal amplitude has been

One female in group I and two in group II had a normal physical working capacity (600 kpm/min) while it was less than normal (900 kpm/min) in all male patients The working capacity was less than 400 kpm/min in women and 600 kpm/min in men in 30 % of the patients in group I—II In group III A 72 % and in group III B 93 % of the patients had a physical working capacity which was lower than these figures

Fig 13 *The relation of the diastolic descent rate of the UCG to the clinical groups (Open circles represent patients with sinus rhythm filled circles patients with atrial fibrillation Horizontal lines represent mean values)*

UCG-FINDINGS The diastolic descent rate was highest in group I—II the difference between the mean values of group I—II and III A was statistically significant However the mean value of group III B was higher than that of III A fig 13

MITRAL VALVE AREAS The mitral valve area estimated by the surgeon was largest in group I—II in the groups

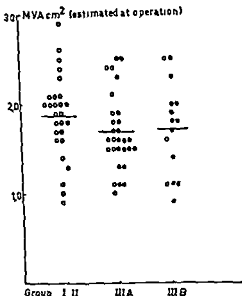

Fig 14 *The relation of the mitral valve area estimated at operation to the clinical groups Symbols as in fig 13*

III A and III B it was of the same order, fig 14 The difference between the mean values of the first two groups was not significant

The area calculated by the Gorlin formula was *much larger in group I—II* than in the other two groups fig 15 and the difference between I—II and III A was statistically significant, (page 48)

HEMODYNAMIC DATA The *cardiac output* both at rest and during exercise decreased with increasing disability The difference between *group I—II and III A* was highly significant at rest and significant during exercise The *stroke volume* showed the same tendency even if the difference between the mean values at rest was only probably significant

The *oxygen consumption* was of the same order in the three groups both at rest and during exercise

The *arterio venous oxygen difference* showed an inverse relationship to the

CHAPTER IV

THE RELATIONSHIP OF CLINICAL DISABILITY TO SOME CLINICAL DATA, UCG-FINDINGS, MITRAL VALVE AREAS AND HEMODYNAMICS

The patients were grouped according to the criteria of the New York Heart Association (74) as modified by BISHOP and WADE (8) and the groups were compared with respect to some clinical data, UCG-findings, mitral valve areas and hemodynamic data (table 11)

The composition of the groups with respect to age and rhythm has been described in chapter I Since group I consisted of only 3 patients these were combined with group II to one group I—II and a statistical evaluation was made of the differences between the mean values of the different parameters in group I—II and III A These two groups were comparable with respect to the number of patients, 27 and 29 respectively, while group III B consisted of only 15 patients

A COMPARISON BETWEEN THE CLINICAL GROUPS I—II, III A AND III B

AGE AND DURATION OF DISEASE The difference in age between the groups I—II and III A was not statistically significant but the mean age increased with increasing disability Nor did the length of time from the first occurrence of rheumatic fever to the operation show any significant difference between the two groups The duration of symptoms also increased with increasing disability the difference between the groups I—II and III A was probably significant

HEART VOLUME The heart volume increased from group I—II to group III B the difference between I—II and III A was probably significant

WORK TEST The heart rate at the lowest work load, 200 kpm/min for women and 300 kpm/min for men, was significantly higher in the patients of group III A than in those of group I—II, in group III B the heart rate was somewhat lower than in III A

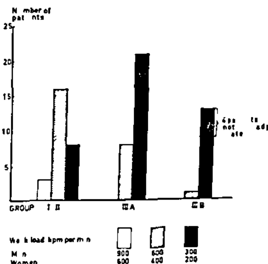

Fig 12 The relation of the physical working capacity to the clinical groups (Work load the highest load at which the patients could perform exercise in a steady state)

Fig 12 shows the distribution of the highest work load which the patients in the different groups could achieve in a steady state As shown by the figure four patients in group III B could not even perform exercise on the lowest load in a steady state

Oxygen consumption (ml/min STPD)												
Rest	25	210	11	23	221	9	10	234	17	19	14	<0 20
Exercise	23	803	31	22	806	37	10	772	40	3	49	>0 90
A – V oxygen difference (ml/l)												
Rest	23	13 4	2 1	25	5? 0	1 9	13	62 4	4 7	8 6	2 9	<0 01
Exercise	23	89 1	3 2	22	111 8	4 0	10	120 8	8 8	22 7	5 2	<0 001
Pressures (Mean pressure mm Hg)												
Brachial artery												
Rest	25	93 1	2 9	26	101 0	2 6	12	111 3	5 8	7 9	3 8	~0 10
Exercise	2?	106 8	3 4	22	109 5	2 8	9	118 9	7 6	2 7	4 4	<0 70
Pulmonary artery												
Rest	27	21 0	1 4	27	31 2	2 2	13	31 0	4 8	10 2	2 6	<0 001
Exercise	25	40 9	2 2	23	58 4	3 6	11	53 5	5 6	17 5	4 8	<0 001
Pulm art wedge												
Rest	27	13 3	1 1	27	19 9	1 4	12	18 7	2 4	6 6	1 8	<0 001
Exercise	24	29 6	2 1	23	38 3	1 9	10	38 3	3 0	8 7	2 8	<0 01
Right atrium												
Rest	17	0 8	0 3	17	2 8	0 6	6	4 2	1 5	2 0	0 7	<0 01
Exercise	23	2 8	0 6	17	6 8	1 0	8	6 8	1 7	4 0	1 2	<0 01
Vascular resistance (units)												
Systemic circulation												
Rest	25	17 6	1 2	25	25 0	1 4	12	30 4	2 4	7 4	1 8	<0 001
Exercise	22	12 1	0 6	22	16 2	1 1	9	18 6	1 0	4 1	1 2	<0 01
Pulmonary circulation												
Rest	25	1 4	0 1	25	2 6	0 3	12	2 4	0 6	1 2	0 3	<0 001
Exercise	22	1 2	0 1	23	2 9	0 4	10	2 9	0 9	1 7	0 4	<0 001

Table 11 *Clinical findings UCG findings mitral valve areas and hemodynamic data in clinical groups I—II III A and III B*

	Group I—II			Group III A			Group III B			Difference I—II — III A		
	n	Mean	± S E	*n*	Mean	± S E	*n*	Mean	± S E	Mean diff	± S E of mean diff	*P*
Age (years)	27	43 7	1 7	29	47 3	1 6	15	50 6	1 7	3 6	2 3	<0 20
Duration (years)												
From rheum fever	18	28 9	1 7	16	29 9	2 9	10	38 1	3 3	0 9	3 4	<0 80
From onset of symptoms	26	5 4	1 1	26	10 7	1 8	14	14 1	2 1	5 4	2 1	<0 05
Heart volume (ml/m² BSA)	27	560	15 4	29	633	26 0	15	730	44 3	73	30 2	<0 05
Work test (Heart rate beats/min)	27	113 5	3 9	29	130 9	4 4	14	128 9	8 2	17 3	5 9	<0 01
UCG												
Descent rate (mm/s)	27	18 2	0 9	29	14 6	0 7	15	16 3	1 3	3 6	1 2	<0 01
Maximal amplitude (mm)	27	20 4	0 8	29	20 1	0 6	15	19 2	1 2	0 3	1 0	<0 80
Mitral valve area (cm²)												
Surgeon s estimate	27	1 87	0 09	29	1 69	0 08	15	1 71	0 13	0 18	0 12	<0 20
Corlin formula	15	1 90	0 17	21	1 16	0 06	8	1 01	0 19	0 74	0 18	<0 001
Cardiac output (Teich l/min)												
Rest	23	5 86	0 13	22	4 21	0 20	10	3 9[illegible]	0 43	1 65	0 47	<0 001
Exercise	23	9 11	0 32	21	7 14	0 37	10	6 52	0 34	1 67	0 48	<0 01
Stroke volume (ml/beat)												
Rest	23	82 1	5 6	22	66 4	5 1	10	56 6	6 6	15 7	7 6	<0 05
Exercise	23	88 2	4 6	21	64 7	4 1	10	[illegible]	4 4	23 5	6 1	<0 001

Oxygen co isun pt on (1 1 11 1 S11 D)									
Rest	9	23	20	14	212	9	23	21	<0 30
I xercise	9	824	55	13	79ɔ	53	29	76	<0 80
(I oxygen d fference (n 1 1)									
Rest	11	47 1	2 9	14	55 9	2 1	8 8	3 6	<0 0ɔ
Exercise	10	96 8	4 8	12	124 3	3 1	27 5	5 7	<0 001
I ressures									
(Mean pressures mm llg)									
B achial artery									
Rest	11	99 4	2 7	15	102 2	4 0	2 8	4 9	<0 60
I xerc e	9	111 6	4 7	13	108 1	3 5	3 5	5 9	<0 60
I ulm nary artery									
Rest	11	32 6	3 2	16	30 1	3 0	2 ɔ	4 4	<0 60
I xercise	10	59 1	4 6	13	57 8	5 5	1 3	7 2	<0 90
I ulm ari wedge									
Rest	11	21 5	1 8	16	18 8	2 0	2 7	2 8	<0 40
I xerc se	10	40 2	2 0	13	36 8	3 0	3 4	3 6	<0 40
R ght atrium									
Rest	7	1 4	0 8	10	3 7	0 7	2 3	1 1	<0 0ɔ
I xercise	5	3 0	0 8	12	8 3	1 2	5 3	1 4	<0 01
I ascul r resistance (u uts)									
Systemic circul t on									
Rest	11	21 2	0 9	11	28 0	2 0	6 8	2 2	0 01
I xerc se	9	13 6	1 1	13	18 0	1 4	4 4	1 8	<0 05
I ul onary circul tion									
Rest	11	2 5	0 5	11	2 8	0 3	0 3	0 6	<0 60
I xerci e	10	2 3	0 6	13	3 3	0 5	1 0	0 8	<0 50

Table 12 *Clinical findings UCG findings mitral valve areas and hemodynamic data in patients of group III A with sinus rhythm and with atrial fibrillation*

	Sinus rhythm			Atrial fibrillation			Difference S R —A F		
	n	Mean	± S E	n	Mean	± S E	Mean diff	±S E of mean diff	P
Age (years)	12	43 6	2 8	17	49 9	1 6	6 3	3 2	<0 10
Duration (years)									
From rheum fever	8	28 6	3 7	8	31 1	4 8	2 5	6 1	<0 70
From onset of symptoms	10	5 1	1 1	16	14 3	2 5	9 2	2 8	<0 01
Heart volume (ml/m² BSA)	12	541	27 0	17	697	32 0	156	41 8	<0 01
Work test (Heart rate beats/min)	12	119 7	7 0	17	138 8	4 9	19 1	8 5	<0 05
UCG									
Descent rate (mm/s)	12	14 3	1 4	17	14 8	0 7	0 5	1 6	<0 80
Maximal amplitude (mm)	12	20 2	0 9	17	20 0	0 8	0 2	1 3	<0 90
Mitral valve area (cm²)									
Surgeon s estimate	12	1 72	0 13	17	1 67	0 10	0 05	0 16	<0 80
Gorlin formula	10	1 21	0 07	11	1 11	0 09	0 10	0 12	<0 40
Cardiac output (Fick l/min)									
Rest	9	4 76	0 29	13	3 83	0 22	0 93	0 36	<0 05
Exercise	9	8 66	0 31	12	6 53	0 44	2 13	0 54	<0 001
Stroke volume (ml/beat)									
Rest	9	66 1	8 8	13	66 6	6 5	0 5	10 9	>0 90
Exercise	9	70 8	4 0	12	60 1	6 3	10 7	7 4	<0 20

arterio venous oxygen difference lower than in those with atrial fibrillation the differences were probably significant at rest and highly significant during exercise The mean *oxygen consumption* at rest and during exercise was of the same order in the two groups of patients

The *pressures* in the systemic and pulmonary circulations were virtually the same in the two rhythms The right atrial pressure was significantly higher in patients with atrial fibrillation In both rhythms the mean values were normal at rest while it was higher than normal in the latter patients during exercise

The *vascular resistance* in the systemic circulation was significantly higher in patients with atrial fibrillation at rest while the difference between the two rhythms during exercise was smaller and only probably significant The mean values of pulmonary vascular resistance did not differ significantly either at rest or during exercise

DISCUSSION

The disability of patients with mitral stenosis has been related to clinical and hemodynamic data in several studies for reference see WADE and BISHOP (92) and WERKO (96) WERKO stressed that most investigators have found a good correlation between the altered hemodynamics and the degree of subjective symptoms though as emphasized by BISHOP and WADE (8) the assessment of disability is largely subjective and therefore as always open to considerable error

The number of patients with atrial fibrillation increased in the groups with more advanced disability in the present study as in other investigations e g ELIASCH (37) BADEN (5) and BISHOP and WADE (8)

The mean age of the *patients with* atrial fibrillation was higher than in those with sinus rhythm BISHOP and WADE (8) also found that within each clinical group patients with atrial fibrillation were on the average older than those with sinus rhythm In BADEN's series (5) of patients with mitral stenosis the incidence of atrial fibrillation increased from 0 % in the age group 10 19 to 75 % in the group 50—59 years

The heart volume increased with the degree of disability, an observation also made by ELIASCH (37) In BADEN's series (5) the large hearts occurred with increasing and the small with decreasing frequency from group II to group IV HUGENHOLTZ et al (56) found that the roentgenological findings did not differentiate between the functional group In the series of HOLMGREN et al (52) the largest heart volumes were found in patients with the lowest physical working capacity

The difference in heart volume between the groups in the present series would be due to the presence of more patients with atrial fibrillation in groups III A and B the mean heart volume of these patients in group III A was also significantly larger than that of patients with sinus rhythm GRANATH (45) found a significantly larger mean heart volume in patients with atrial fibrillation while VARNAUSKAS et al (91) found only a little larger heart size in atrial fibrillation than in sinus rhythm

The need for more objective methods for determining the functional incapacity than that attained by the clinical classification was stressed by HOLMGREN *et al* (52) in their study of the physical working capacity in patients with mitral valvular disease WERKO (96) however was of the opinion that the calculating of the physical working *capacity from* the pulse rate during exercise did not add further information *to the* evaluation of the patients with mitral stenosis

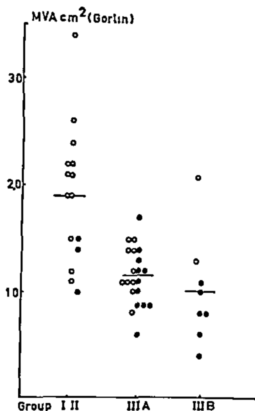

Fig 15 *The relation of the mitral valve area calculated by the Gorlin formula to the clinical groups Symbols as in fig 13*

cardiac output and increased with increasing disability Statistically significant differences were shown to exist between the mean values of the groups I—II and III A both at rest and during exercise

The *mean pressure in the systemic circulation* showed a small and insignificant increase from group I—II to group III B both at rest and during exercise

The *mean pressures in the pulmonary artery and in the pulmonary arterial wedge position* were lower in group I—II than in the other two groups both at rest and during exercise The differences between group I—II and III A were significant or highly significant

The mean values of the *pressure in the right atrium* were within the normal range at rest in all the three groups but the difference between I—II and III A was statistically significant During exercise the mean values were higher than normal in the groups III A and III B while it was normal in I—II

The calculated *vascular resistances* in the systemic and pulmonary circulation were significantly lower in group I—II than in the groups III A and III B

THE RELATIONSHIP OF THE HEART RHYTHM TO THE DIFFERENT PARAMETERS IN GROUP III A

The three groups of patients showed great differences with respect to the heart rhythm the number of patients with sinus rhythm decreased from 89 % in group I—II to 41 and 20 % respectively in groups III A and III B

The influence of the heart rhythm was studied by a statistical analysis of the differences between the mean values of the same parameters as above in the patients with sinus rhythm and with atrial fibrillation in group III A (table 12)

The mean *age* of the patients with atrial fibrillation was higher, but the difference was not statistically significant The *duration of symptoms* was significantly longer in patients with atrial fibrillation The *heart volume* was significantly larger in patients with atrial fibrillation

At the *work test* the mean heart rate at the lowest load was higher in patients with atrial fibrillation the difference was probably significant Five patients with sinus rhythm and three with atrial fibrillation could perform exercise in a steady state on the second load 100 kpm/min for women and 600 kpm/min for men

The *UCG findings* and the *mitral valve areas* estimated at the operation and calculated by the Gorlin formula showed small and insignificant differences between the two rhythms

In patients with sinus rhythm the *cardiac output* was higher and the

following chapter It should only be pointed out that patients with slight disability can have small mitral orifices while incapacitated patients can be found at operation to have relatively large valve areas in the latter case no great relief of symptoms is to be expected after a mitral valvulotomy

HUGENHOLTZ et al (56) studied the relation of the clinical disability to the mitral valve area calculated by the Gorlin formula which they had found to show a good agreement with the area estimated at operation The mitral valve area decreased with increasing disability from group I to group III the mean area was 1 8 cm² in group I and 1 4 respectively 0 9 cm² in group II and III However the often poor relationship between disability and the degree of stenosis was shown by the finding of 14 of 20 patients in group II who had valve areas of the same size (less than 1 5 cm²) as the patients in group III

While the oxygen consumption at rest and during exercise was the same in the three groups the cardiac output decreased and the arterio venous oxygen difference increased with increasing disability The differences between groups I II and III A were statistically significant These findings are consistent with the observations made by ELIASCH (37) who also found a significantly higher cardiac output and a lower arterio venous oxygen difference at rest in *group I—II than in group III The mean* values of the cardiac index in the present series 3 42 l min m² in group I—II and 2 48 in group III A were virtually the same as those in ELIASCH s material 3 78 respectively 2 69 l/min/m² WADE and BISHOP (92) found no significant difference in cardiac index between the groups I II and III A but on the other hand the cardiac index was somewhat higher in the latter than in the former group WERKO (96) found higher mean values of cardiac output at rest and during exercise in the patients of group I—II than in those of group III In the series of HUGENHOLTZ et al (56) the mean cardiac index showed but slight differences between the different groups of patients

The variability in the relation between the graded clinical disability and the cardiac output in different investigations might be due to the varying frequency of patients with atrial fibrillation in the clinical groups

In the present series the mean mitral valve areas estimated by the surgeon and by the Gorlin formula showed only small differences between the two rhythms in the patients of group III A, yet the cardiac output was significantly higher and the arterio venous oxygen difference lower in the patients with sinus rhythm

ELIASCH (37) compared the hemodynamics at rest in patients with sinus rhythm and with atrial fibrillation in group III and found a significantly higher cardiac index and a probably significantly lower arterio venous oxygen difference in the patients with sinus rhythm In the series of WADE and BISHOP (92) the resting cardiac index was significantly higher in patients with sinus rhythm in all the clinical groups

The mean pressures in the pulmonary artery and in the pulmonary arterial wedge position were significantly higher in group III A than in group I—II both at rest and during exercise In ELIASCH s study (37) the mean resting pulmonary arterial and "pcv" pressures were 18 8 and 12 5 *mm Hg respectively in group* I—II and 33 6 20 4 mm Hg respectively in group III Virtually the same values were observed in the present series

BISHOP and WADE (8) concluded that the grade of disability was related to the level of pulmonary arterial mean pressure both at rest and during exercise yet no significant difference in pulmonary arterial pressure was found between

In the present study the mean heart rates at the lowest work load in the different groups were compared, as well as the number of patients in the groups who could achieve higher work loads in a steady state. Thus the physical working capacity was not determined as the estimated work load at the heart rate of 170 beats per minute as in the study of HOLMGREN et al (52). The use of the heart rate at a certain load for measuring of the physical working capacity in patients with atrial fibrillation has been discussed. HOLMGREN et al (52) found a linear relationship between heart rate and work load even in cases with atrial fibrillation, while WERKO (96) stressed that some patients with atrial fibrillation react during exercise with an increase in heart rate "up to a maximal level" on a slight work load though they then are able to perform more strenuous exercise without further increase of the heart rate.

In the present series the mean heart rates at the lowest work load were higher in the groups with more advanced disability than in group I—II, the percentage of patients not being able to perform work at more than the lowest work load increased from group I—II to group III B. Thus the physical working capacity was related to the grading of the disability obtained by the history.

The heart rate in patients with sinus rhythm in group III A was lower than in those with atrial fibrillation in the same group, however, the difference was only probably significant. GRANATH (45) found higher maximal work intensity in patients with sinus rhythm than in those with atrial fibrillation in both men and women but the differences were not significant.

The relation of the rate of diastolic descent in the UCG tracing to the degree of clinical disability was also studied by EFFERT (33). The highest mean value, 34 mm/s (range 30—48), was found in the patients of *group I*. The mean descent rate in group II, 16.5 mm/s, was higher than that of group III, 10.6 mm/s, and of group IV, 11.2 *mm/s. The number of patients in* the different groups was not reported and no statistical evaluation of the differences between the groups was performed. Very low descent rates, 4 mm/s, were found in all but the first group.

In the present series the mean rate of descent was highest in the group with the least disability, namely group I—II. The difference between this group and group III A was statistically significant, however, the difference was less between the first group and group III B. As shown by fig. 13 the majority of patients with a descent rate of 20 mm/s or more had sinus rhythm and belonged to functional group I—II, while the rate exceeded this figure in only one patient *of group III A. The three patients with* atrial fibrillation in group I—II had descent rates of more than 16 mm/s. However, seven patients with sinus *rhythm in group I—II had a descent* rate of less than 15 mm/s. The pattern of the descent rate in group III B was more heterogeneous than in the other two groups.

The mitral valve area estimated at operation was largest in the group with the least incapacitated patients but no significant differences were found between the groups. On the other hand the valve area calculated on the basis of hemodynamic data showed a highly significant difference between the groups I—II and III A while the mean calculated areas were of the same order in the groups III A and III B.

The relationship between valve areas estimated at operation and those calculated by the Gorlin formula as well as the correlations of these areas to the UCG findings will be discussed in the

following chapters It should only be pointed out that patients with slight disability can have small mitral orifices while incapacitated patients can be found at operation to have relatively large valve areas, in the latter case no great relief of symptoms is to be expected after a mitral valvulotomy

HUGENHOLTZ et al (56) studied the relation of the clinical disability to the mitral valve area calculated by the Gorlin formula which they had found to show a good agreement with the area estimated at operation The mitral valve area decreased with increasing disability from group I to group III the mean area was 1 8 cm in group I and 1 4 respectively 0 9 cm^2 in group II and III However the often poor relationship between disability and the degree of stenosis was shown by *the finding of 14 of 20 patients* in group II who had valve areas of the same size (less than 1 5 cm) as the patients in group III

While the oxygen consumption at rest and during exercise was the same in the three groups the cardiac output decreased and the arterio venous oxygen difference increased with increasing disability The differences between groups I—II and III A were statistically significant These findings are consistent with the observations made by ELIASCH (37) who also found a significantly higher cardiac output and a lower arterio venous oxygen *difference* at rest in group I II than in group III The mean values of the cardiac index in the present series 3 42 l min m^2 in group I—II and 2 48 in group III A were virtually the *same as those in* ELIASCH's material 3 78 respectively 2 69 l/min/m^2 WADE and BISHOP (92) found no significant difference in cardiac index between the groups I—II and III A but on the other *hand the cardiac index was somewhat* higher in the latter than in the former group WERKÖ (96) found higher mean values of cardiac *output at rest* and during exercise in the patients of group I—II than in those of group III In the series of HUGENHOLTZ et al (56) the *mean* cardiac index showed but light differences between the different groups of patients

The variability in the relation between the graded clinical disability and the cardiac output *in different investigations* might be due to the varying frequency of patients with atrial fibrillation in the clinical groups

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The mean pressures in the pulmonary artery and in the pulmonary arterial wedge position were significantly higher in group III A than in group I—II both at rest and during exercise In ELIASCH's study (37) the mean resting pulmonary arterial and 'pcv' pressures were 18 8 and 12 5 mm Hg respectively in group I—II and 33 6 20 4 mm Hg respectively in group III Virtually the same values were observed in the *present series*

BISHOP and WADE (8) concluded that the grade of disability was related to the level of pulmonary arterial mean pressure both at rest and during exercise yet no significant difference in pulmonary arterial pressure was *found* between

their groups I—II and III A The pulmonary arterial wedge pressure in their study did not show any significant difference between the groups except for a probably significant difference between the patients with sinus rhythm in group I—II and those with atrial fibrillation in group III A

HUGENHOLTZ et al (56) compared patients from group I—II who had valve areas of 1 5 cm² or less with the patients from group III having valve areas of this size The mean left atrial pressures and the mean left atrial—left ventricular diastolic gradients did not show any significant differences between the two groups of patients, however, the mean pulmonary arterial pressure in the patients of group III was significantly higher than that of group I—II

The lack of significant differences in pulmonary arterial and wedge pressures between patients with sinus rhythm and with atrial fibrillation in group III A of the present series agrees with the findings of ELIASCH's group III patients (37) The level of the mean pressures in the two rhythms observed in the present series corresponds well to those found by ELIASCH

The calculated vascular resistances within the systemic and the pulmonary circulations were significantly higher in group III than in group I—II while the levels of resistances in groups III A and III B were of the same magnitude In group I—II the mean value of pulmonary vascular resistance was lower during exercise than at rest while the relation between rest and exercise values in group III A and III B was reversed

ELIASCH (37) also found significantly higher pulmonary and systemic vascular resistance at rest in group III than in group I—II The former resistance was significantly higher in group III than in group I—II in HUGENHOLTZ's series (56)

When ELIASCH compared patients with sinus rhythm and with atrial fibrillation in group III he found a significantly higher systemic vascular resistance in the latter patients while the pulmonary vascular resistance did not differ significantly between the two rhythms In the present study the same observation was made

REALE (77) in a recent study compared the hemodynamics immediately before and after countershock conversion of atrial fibrillation in 12 patients with mitral valvular disease, in most patients both the pulmonary and systemic vascular resistances decreased after conversion to sinus rhythm

SUMMARY

The clinical disability of the 71 patients in the present study was assessed by the criteria of New York Heart Association modified by BISHOP and WADE Three groups, I—II (27 patients), III A (29) and III B with 15 patients were compared with respect to some clinical data, heart volume, physical working capacity, UCG findings, mitral valve areas and hemodynamics, the differences between the first two groups were statistically evaluated

The physical working capacity was related to the clinical disability the heart rate at the lowest work load was higher in the groups with more advanced disability and the percentage of patients not being able to perform work at more than the lowest load increased from group I—II to group III B

The diastolic descent rate of the UCG tracing was higher and the mitral valve area calculated by the Gorlin formula was significantly larger in group I—II than in group III A The mitral valve area estimated at operation did not show any significant difference between these two groups areas about 1 cm² were found even in patients of group I—II

Cardiac output and arterio venous oxygen difference at rest and during exercise showed significant differences between the two groups, the former being lower and the latter higher in group III A

The pulmonary arterial and wedge pressures were significantly higher in group III A as also were the vascular resistances within the systemic and pulmonary circulations

Patients with sinus rhythm and with atrial fibrillation in group III A were also compared The UCG-findings the mitral valve areas and the pressures in the pulmonary circulation were virtually the same in the two rhythms while significant differences were found with respect to heart volume, heart rate during work test, cardiac output and arterio venous oxygen difference The systemic vascular resistance was significantly higher in atrial fibrillation while the pulmonary vascular resistance showed no significant difference between the two rhythms

their groups I—II and III A The pulmonary arterial wedge pressure in their study did not show any significant difference between the groups except for a probably significant difference between the patients with sinus rhythm in group I—II and those with atrial fibrillation in group III A

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SUMMARY

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The diastolic descent rate of the UCG tracing was higher and the mitral valve area calculated by the Gorlin formula was significantly larger in group I—II than in group III A The mitral valve area estimated at operation did not show any significant difference between these two groups areas about 1 cm² were found even in patients of group I—II

second group Even if the difference was statistically significant the separation between the groups was not so distinct as with respect to valve areas estimated at operation The calculated area was less than 1 5 cm² in all but one patient of the first group but it was of the same order in six patients belonging to the second group (fig 17)

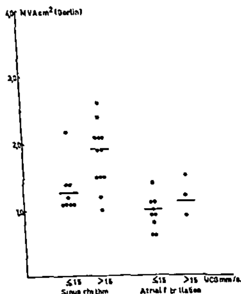

Fig 17 *The relation of the calculated mitral valve area to the two groups of descent rate*

The *oxygen consumption* at rest and during exercise did not differ significantly between the two groups nor did the *cardiac output* at rest and during exercise (The difference in *cardiac index* at rest between the groups 2 89 respectively 3 6 l/min/m² was probably significant) Fig 18 illustrates the uniform distribution of the cardiac output during exercise in the two groups

The mean values of *stroke volume* at rest and during exercise did not show any significant differences between the two groups In both groups the mean exercise values were somewhat higher than the mean values at rest Fig 19 a illustrates the change in stroke volume from rest to exercise In most patients it increased slightly during exercise, in 2 of 11 patients of the first group and in 7 of 17 patients of the second group the stroke volume decreased The greatest change was observed in two patients

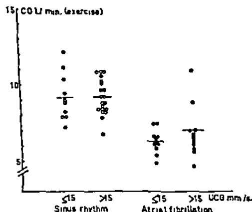

Fig 18 *The relation of the cardiac output (Fick) during exercise to the two groups of descent rate*

of the second group cases 111 and 109, where the stroke volume decreased from 150 and 140 ml at rest to 98 and 88 ml respectively during exercise The first patient was presumably not in a steady state at rest with an oxygen consumption of 403 ml/min the second showed a hyperkinetic circulation at rest with a low arterio venous oxygen difference 23 ml/l

The *arterio venous oxygen difference* was lower in patients with a descent rate exceeding 15 mm/s both at rest and during exercise, however the differences were only probably significant Fig 20 shows that the arterio venous oxygen difference during exercise was less than 75 ml/l in three patients, two of these had a descent rate of 23 mm/s while it was 18 mm/s in the third it was about

CHAPTER V

UCG-FINDINGS IN RELATION TO CLINICAL, HEMODYNAMIC AND SURGICAL FINDINGS — A COMPARISON BETWEEN PATIENTS WITH A RATE OF DIASTOLIC DESCENT MORE OR LESS THAN 15 mm/s

The diastolic descent rate of the UCG tracing in the present series ranged between 8 and 27 mm/s with a *mean value* of 17 0 mm/s in patients with sinus rhythm and 15 5 *mm/s* in those with atrial fibrillation

The validity of the UCG in estimating the degree of mitral stenosis was tested by comparing the mean values of some data in patients showing a *descent rate* of 15 mm/s or less with the corresponding values in patients with a descent-rate exceeding this figure

Patients with sinus rhythm and atrial fibrillation were compared separately, a comparison was also made between patients belonging to the same group with respect to rate of descent but with different heart rhythm (table 13 and 14)

PATIENTS WITH SINUS RHYTHM

The *descent rate* was 15 mm/s or less in 16 patients (range 7—15 mm/s) while the rate exceeded this figure in 23 patients (range 16—26 mm/s) The difference between the mean values of the groups was statistically significant The *maximal amplitude* of the UCG tracing was also significantly lower in the first group

The mean values of *age, duration of symptoms, heart volume* and *heart rate at the lowest work load* did not show any significant differences between the two groups

The average *mitral valve area* estimated by the surgeon was significantly smaller in the group with the lower *descent rate* Fig 16 shows that the valve area was 1 5 cm² or less in nine of these patients and that it was less than 2 cm² in all but two patients On the other hand the area was larger than 1 5 cm² *in all patients* having a rate of *descent exceeding* 15 mm/s In more than half of these patients the valve area was 2 cm² or larger

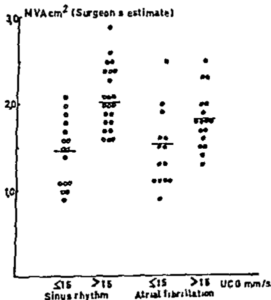

Fig 16 *The relation of the mitral valve area estimated at operation to the two groups of descent rate (Horizontal lines represent mean values)*

The mitral valve area was calculated by the Gorlin formula in nine patients of the first group and in fifteen of the

Ox g n on un j o												
(n l STI (l)												
Re t	13	21ɔ	16	?0	233	13	14	231	10	11	210	13
I xerc e	11	887	51	20	77ɔ	28	12	79ɔ	29	12	763	61
A I oxygen d ff en e (nl l)												
Rest	14	4 9	1 5	19	39 5	2 3	14	63 0	3 8	14	57 6	2 2
I xe e	12	99 7	4 4	20	85 8	2 9	11	131 6	5 9	12	113 1	4 9
I ressures												
(Mean j es u es r Hg)												
B a h al a t ry												
Rest	14	93 9	4 0	21	97 9	3 1	1ɔ	107 9	1 9	13	100 1	4 3
I xerc e	12	109 1	5 4	18	109 8	3 7	11	111	5 8	12	109 8	1 3
I ulmon y a t ry												
Rest	1ɔ	30 9	2 9	22	20 6	1 2	15	31 5	3 9	15	2ɔ 1	3 2
I xerc se	13	58 6	3 7	21	40 1	2 2	12	61 0	5 3	13	47 4	5 2
I uln a t edge												
Rest	15	20 1	1 9	22	12 9	1 0	14	19 9	1 9	15	16 9	2 3
I xe c e	13	39 8	2 6	21	29 2	1 9	12	39 2	3 1	11	33 9	3 1
R ght a an												
Re t	8	0 8	0 (	15	0 9	0 4	11	3 9	0 8	6	3 7	1 2
I xerc se	8	4 0	1 2	18	1 8	0 6	10	8 3	1 4	12	7 1	1 0
I a ul r res s a es (ts)												
Sys em c cul on												
Rest	14	19 ?	1 ?	21	17)	1 3	15	29 9	2 2	1?	27 9	2 0
I xerc e	12	12 8	1 0	18	12 5	0 6	11	19 1	1 4	12	16 9	1 4
I ulmona y c cula on												
Rest	14	? 2	0 1	21	1 1	0 2	11	3 2	0 ɔ	13	1 8	0 3
I xerc e	1?	2 3	0 ɔ	20	1 ?	(1	1	3 0	0 8	11	2 3	0 4

Table 13 *Mean values of some data in the two groups of descent rate*

	Sinus rhythm						*Atrial fibrillation*					
	≤ 15 mm/s			> 15 mm/s			≤ 15 mm/s			> 15 mm/s		
	n	Mean	± S E	*n*	Mean	± S E	*n*	Mean	± S E	*n*	Mean	± S E
Age (years)	16	44 4	2 1	23	43 5	1 9	15	51 1	1 7	17	48 9	1 7
Duration (years)												
From rheum fever	12	28 8	2 8	13	29 5	1 9	8	37 0	5 4	11	32 4	2 9
From onset of symptoms	16	4 6	1 0	20	5 2	1 1	13	16 2	2 6	17	13 4	2 0
Heart volume (ml/m² BSA)	16	566	20 8	23	543	17 0	15	781	35 2	17	656	33 6
Work test (Heart rate beats/min)	16	112 6	6 0	23	119 6	4 1	14	131 4	7 9	17	133 8	5 9
UCG												
Descent rate (mm/s)	16	11 6	0 6	23	20 7	0 7	15	12 3	0 7	17	18 2	0 5
Maximal amplitude (mm)	16	17 6	1 0	23	21 6	0 6	15	18 9	1 2	17	21 2	0 8
Mitral valve area (cm²)												
Surgeon's estimate	16	1 46	0 10	23	2 08	0 08	15	1 53	0 13	17	1 82	0 08
Gorlin formula	9	1 27	0 13	15	1 91	0 16	11	0 99	0 08	9	1 10	0 13
Cardiac output (Fick l/min)												
Rest	13	5 15	0 31	18	6 04	0 50	13	3 80	0 25	11	3 80	0 31
Exercise	11	9 06	0 47	20	9 09	0 26	11	6 22	0 24	12	6 77	0 47
Stroke volume (ml/beat)												
Rest	13	78 4	7 2	18	76 7	7 2	13	67 2	7 6	11	58 6	3 6
Exercise	11	86 0	7 7	20	80 6	4 5	11	61 5	6 6	12	59 2	3 8

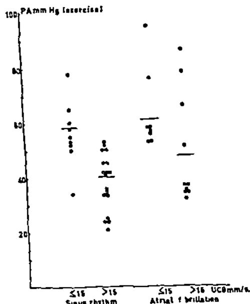

Fig 21 *The relation of the pulmonary arterial mean pressure during exercise to the two groups of descent rate*

Fig 22 shows the distribution of the pulmonary arterial wedge pressures during exercise in the two groups two of thirteen patients in the first group had pressures less than 30 mm Hg while it was below this value in about half of the patients in the second group On the other hand the pressure was more than 40 mm Hg in seven patients of the first group while it exceeded this value in only two patients of the second group

The mean values of *right atrial pressure* at rest and during exercise were within the normal range in both groups of patients and no significant differences were found

The calculated *vascular resistance* in the systemic circulation showed no significant difference between the two groups The mean values of pulmonary vascular resistance were slightly elevated in the first group in the second they were within the normal range However it was only during exercise that the difference was probably significant In the first group five patients had resistance values of 2 units or more at rest, the highest value was 6 8 units In the group with the higher descent rate the resistance was less than 2 units in all but two patients Fig 23 a illustrates the calculated pulmonary vascular resistance in those patients where it was determined at rest and during exercise In the group with the lower descent rate the resistance increased during exercise in eight of twelve patients, in four it exceeded 2 units A small increase in resistance during exercise was observed in six of twenty patients in the second group in only one patient did it exceed 2 units (Page 60)

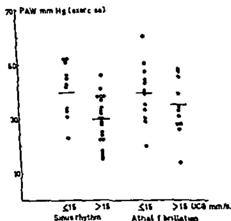

Fig 22 *The relation of the pulmonary arterial wedge pressure during exercise to the two groups of descent rate*

PATIENTS WITH ATRIAL FIBRILLATION

In fifteen patients the diastolic *descent rate* was 15 mm/s or less (range 11—15 mm/s) while it exceeded this figure in seventeen patients (range 15—22 mm/s) the mean difference between the groups was statistically significant No significant differences were found with respect to *maximal amplitude* of the UCG

SV ml/L

150

100

50

R E R E

≤15 mm/s >15 mm/s

a) Sinus rhythm

SV ml/l

150

100

50

R E R E

≤15 mm/s >15 mm/s

b) Atrial fibrillation

Fig 19 *The change of the stroke volume from rest (R) to exercise (F) in the two groups of descent rate a) patients with sinus rhythm b) patients with atrial fibrillation*

125 ml/l in two patients having descent rates of 12 and 13 mm/s

While the differences in blood flow between the groups were small the reverse was true of the *pressures in the pulmonary circulation* The pulmonary arterial and the pulmonary arterial wedge pressures, both at rest and during exercise, were significantly higher in the group of patients having a descent rate of 15 mm/s or less Fig 21 illustrates the mean pressures in the pulmonary artery during exercise in the two groups In the first group the pressure was less than 40 mm Hg in only one patient while eight patients in the second group had pressures below this value In the first group six patients had pressures of 60 mm Hg or more while the pressure did not reach this value in any of the patients in the second group

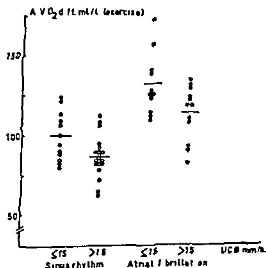

Fig 20 *The relation of the arterio-venous oxygen difference during exercise to the two groups of descent rate*

volume decreased during exercise in all but two of the former patients (three patients with a resting stroke volume above 100 ml had a heart rate below 60 beats/min) In the second group five patients showed a small increase in stroke volume during exercise while it decreased slightly in the others

The *arterio venous oxygen difference* was higher in the group with the lower descent rate both at rest and during exercise, but the mean differences were not significant It was 140 ml/l or more in three patients during exercise (fig 20) these had a descent rate between 11 and 13 mm/s and valve areas about 1 cm² according to the surgeon

The mean *pulmonary arterial pressures* at rest and during exercise were on the average higher in the group with the lower descent rate but the differences between the means were not significant (When the difference between the pressures during exercise was tested by Wilcoxon's test it was probably significant $p < 0.05$) Four patients in the first group had mean pressures above 70 mm Hg during exercise a pressure of the same order was observed in two patients of the second group fig 21 This figure also shows that the mean pressure was below 40 mm Hg in only one patient of the first group while seven patients of the second group had mean pressures below this value during exercise

The difference in *pulmonary arterial wedge pressures* between the groups was even less Fig 22 illustrates that the mean pressures during exercise were evenly distributed between 25 and 50 mm Hg in most of the patients in the two groups One patient with an extremely high pressure 60 mm Hg had a descent rate of 11 mm/s

The *right atrial pressure* was of the same order in the two groups Two patients in the first and one in the second group had pressures above 6 mm Hg at rest during exercise it exceeded this value in five patients of the first and in three patients of the second group

The calculated *pulmonary vascular resistance* was on the average higher in patients with a descent rate of 15 mm/s or less The mean values were above the normal limit both at rest and during exercise The difference between the groups was probably significant at rest Fig 23 b illustrates that in the first group six patients showed a definite increase in resistance during exercise in three the values decreased while two patients showed no change between rest and exercise In the second group the resistance increased more than 1 unit during exercise in two patients while it showed a small increase or no change in seven patients and a decrease in two The figure also shows that the highest resistance values were found within the first group thus four patients in the first group in contrast to one in the second had resistance values above 4 units during exercise

A COMPARISON BETWEEN PATIENTS WITH SINUS RHYTHM AND WITH ATRIAL FIBRILLATION

The mean differences between patients with sinus rhythm and with atrial fibrillation belonging to the first and the second groups respectively (as regards descent rate) were calculated and statistically evaluated (table 14)

In the groups with the lower descent rate the *age* was probably significantly higher in patients with atrial fibrillation The average *duration of symptoms* was significantly longer in patients with atrial fibrillation within both groups of descent rate

The *heart volume* was significantly larger in patients with atrial fibrillation, the difference was greatest between the groups with the lower descent rate

In the *work test* patients with atrial fibrillation had a higher mean heart

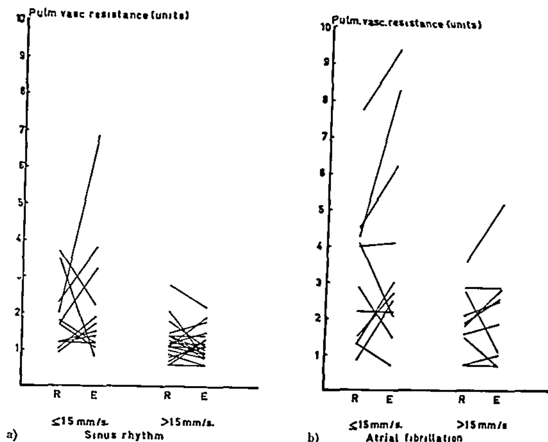

Fig 23 *The change of the calculated pulmonary vascular resistance from rest (R) to exercise (E) in the two groups of descent rate a) patients with sinus rhythm b) patients with atrial fibrillation*

tracing, *age*, *duration of symptoms* and *time from rheumatic fever*

The mean *heart volume* was larger in the first group but the difference was not significant The *heart rate at the lowest work load* was of the same order in the two groups

The mean value of the *mitral valve area* estimated by the surgeon was smaller in the first group but the difference between the groups was not significant Fig 16 shows that nine patients of the first group had valve areas of 1 5 cm² or less while four patients in the second group had areas of the same size One patient of the first and three patients of the second group had valve areas exceeding 2 cm²

The overlap between the groups was even more marked with respect to mitral valve areas calculated by the Gorlin formula which is illustrated by fig 17 The mean values of the groups were virtually the same and half of the patients in each group had valve areas of 1 0 cm² or less

The *oxygen consumption*, the *cardiac output* and the *stroke volume* at rest and during exercise showed small and in significant mean differences between the two groups Fig 18 shows that most of the patients had a cardiac output of less than 7 l/min during exercise The oxygen consumption was 1300 ml/min in the only patient which had a cardiac output more than 10 l/min

Fig 19 b illustrates the stroke volume at rest and during exercise in ten patients of the first and in eleven patients of the second group The stroke

ok lun												
R	1 7	10		8	8 1		11 2	10 5	0 0	18 1	8 1	~0 0
I	[illegible]	8 8		3	7 7		21	10 1		21 1	5 9	<0 01
O -cons												
R	1[illegible]	[illegible]		[illegible]	17		11	19	—	23	18	—
I	11[illegible]	58		32	68		92	59	—	1[illegible]	67	—
I O₁d ff												
R	[illegible]	[illegible]8	0 0	[illegible]	1 1	0 05	17 1	1 1	<0 001	18 1	3 2	<0 001
I	13 [illegible]	5 3	0 0	18	7 7		31 9	7 1	0 001	27 3	5 7	<0 001
I e u es												
R I												
R	1 0	1		7 8	[illegible]		11 0	6 3	0 0	[illegible]	3	—
I	0 7	6 6		1 7	7		4	8[illegible]	—	0 0	5 7	—
I 1												
R	10 3	3 2	0 01	9 1	1		3 6	4 9		1	3	—
I	18	1 4	0 001	13 6	7 5		2 1	6 5		7 3	5 7	—
I A II												
R	7 5	2 1	01	3 0	3 1		0 5	2 7	—	1	3	—
F	10 6	3 3	0 01	5 3	1 1		0 6	1 1	—	1 7	3 7	—
R I												
R	0 2	0 7		0[illegible]	1 1		3 2	1 0	<0 01	[illegible]7	1 3	<0 05
I	2[illegible]	1 3		1[illegible]	1 8	—	4 3	1 8	<0 05	5 3	1 2	<0 001
Iate res												
Sys e												
R	1 3	1 7		[illegible]0	3		1 7		[illegible] 1	10 1	[illegible]1	0 0 1
J	0 3	1[illegible]		2 2	1 9		[illegible] 3	1 7	<0 01	1 1	1 5	<0 01
I lm e c												
R	0 8	0 5		1 1		<0 0	1 0	0 7	—	0 1	0 3	—
I	1 1	[illegible] 5	0	1	0 9	—	1 5	0 9	—	1 1	0 1	<0 05

Table 14 *Mean differences of the data in table 13 (between the two groups of descent rate in patients with sinus rhythm (S R) and with atrial fibrillation (A F) and between patients belonging to the same group of descent rate but with different heart rhythm)*

	Sinus rhythm Diff ≤ 15 mm/s — > 15 mm/s			*Atrial fibrillation* Diff ≤ 15 mm/s — > 15 mm/s			*Diff S R ≤ 15 mm/s — A F ≤ 15 mm/s*			*Diff S R > 15 mm/s — A F > 15 mm/s*		
	Mean diff	± S E of mean diff	*P*	Mean diff	± S E of mean diff	*P*	Mean diff	± S E of mean diff	*P*	Mean diff	± S E of mean diff	*P*
Age	0 9	2 9	—	2 2	2 4	—	6 7	2 7	< 0 05	5 4	2 6	—
Duration												
Rheum	0 7	3 4		4 6	6 1	—	8 2	6 1	—	2 9	3 5	—
Sympt	0 6	1 5		2 8	3 3	—	11 6	2 8	<0 001	8 2	2 3	<0 01
Heart vol	23	26 8		125	48 6	<0 05	215	40 9	<0 001	113	37 6	<0 01
Work test	7 0	7 1	—	2 4	9 8	—	18 8	9 9	—	14 2	7 2	—
UCG												
Descent rate	9 1	0 9	0 001	5 9	0 8	<0 001	0 7	0 9	—	2 5	0 8	<0 01
Max ampl	4 0	1 6	0 001	2 3	1 4	—	1 3	1 6	—	0 4	1 0	—
MF I												
Op	0 62	0 12	0 001	0 29	0 15	—	0 07	0 16	—	0 26	0 11	<0 05
Corlin	0 64	0 21	0 01	0 11	0 15		0 28	0 15	—	0 81	0 21	<0 001
Cardiac output												
R	0 89	0 59		0 00	0 40		1 35	0 40	<0 01	2 24	0 59	< 0 001
I	0 03	0 54		0 55	0 53		2 84	0 52	<0 001	2 32	0 54	<0 001

ence found during exercise Fig 23 shows that the highest resistance values were found in patients with atrial fibrillation

The mean values of *right atrial pressures* were higher in patients with atrial fibrillation Significant differences between the two rhythms were found at rest in patients with the lower descent rate and during exercise in the groups with descent rates above 15 mm/s All patients with sinus rhythm had a right atrial pressure below 6 mm Hg at rest it exceeded this value in three patients with atrial fibrillation During exercise two patients with sinus rhythm and eight patients with atrial fibrillation had mean pressures above this figure

DISCUSSION

The diagnosis of mitral stenosis by auscultation alone does not generally cause any difficulties However as stated by e g LIKOFF (65) the mere presence of anatomic mitral stenosis is not an indication for operation the need for surgery is determined by the pathophysiological evaluation This evaluation is often made on the basis of physical signs and the symptoms of the patient But severe mitral stenosis can be found in a nearly asymptomatic state as pointed out by HUGENHOLTZ et al (56)

Hemodynamic studies are usually of great value in estimating the degree of stenosis However ELLIS and ADLER (40) among others considered that these methods also have definite limitations because of many variants in the complicated interaction of blood flow and pressures which may change rapidly from moment to moment During recent years several authors have emphasized that an estimate of the degree of obstruction requires a knowledge of the pressure flow relations across the tenotic mitral valve e g DICKENS et al (18) This necessitates combined right and left heart catheterization a method which is not without risks for the patient

Since the introduction of ultrasoundcardiography this method has been used for the preoperative evaluation of mitral stenosis Earlier reports by e g EDLER and GUSTAFSON (29) and EFFERT (33) have shown that the method is of definite value in estimating the degree of stenosis According to EFFERT et al (34) the clinical examination and the UCG make it possible to decide whether surgery is indicated in 97 % of all cases of mitral stenosis

However, the relation between UCG findings and the degree of mitral stenosis estimated by other methods has hitherto been incompletely investigated The present part of the author s study was performed to investigate how well a certain value of the rate of diastolic descent in the UCG tracing separates cases of mitral stenosis of different severity defined by clinical, hemodynamic and surgical findings The figure 15 mm/s was chosen on the basis of earlier experience and after a preliminary survey of the present material In the study of EDLER and GUSTAFSON (29) the mean value of descent rate was 13 mm/s in mitral stenosis admitting one fingertip at operation in stenosis admitting one finger it was 17 mm/s

When studying the results of this comparison between patients with different descent rates it must be remembered that the present material is a selected one in so far as it comprises only patients in which the degree of mitral stenosis was estimated at operation Thus patients with mitral stenosis of so slight a degree that operation was not indicated are not included

Concerning the patients with sinus rhythm it was found that the descent rate of 15 mm/s fairly well separated patients with advanced stenosis from those in which it was of moderate or slight degree Thus all patients with

rate than those with sinus rhythm but the mean differences between the groups were not significant

The mean values of *descent rate* did not differ significantly between the two rhythms in the first group but in the second group patients with atrial fibrillation had a significantly lower descent-rate

The *mitral valve areas* did not differ significantly between the heart rhythms when patients with descent rate within the lower range were compared, fig 16 and 17 The mean valve areas of patients with atrial fibrillation were smaller than those of patients with sinus rhythm in the groups with descent rates exceeding 15 mm/s The difference in surgically estimated valve area was small and only probably significant whereas the difference in areas calculated by the Gorlin formula was much greater and highly significant No patient with atrial fibrillation in the group with the higher descent rate had a valve area of more than 2 cm² while areas of this size were found in seven patients of the corresponding group with sinus rhythm, fig 17

The *cardiac output* was significantly higher in the patients with sinus rhythm, both at rest and during exercise, while the oxygen consumption was insignificantly higher in these patients When the groups with the lower descent rate were compared it was found that the highest values of cardiac output during exercise in patients with atrial fibrillation were on the same level as the lowest values found in patients with sinus rhythm, fig 18 This figure also shows that only one patient with atrial fibrillation in the second group had a cardiac output above the mean value of the corresponding patients with sinus rhythm

The mean *stroke volume* at rest and during exercise was larger in the patients with sinus rhythm, however, the only significant difference was found during exercise in the group with a descent rate exceeding 15 mm/s Most patients with sinus rhythm in the group with the lower descent rate showed some increase of the stroke volume from rest to exercise while the reverse was found in the corresponding patients with atrial fibrillation, fig 19 a and b

The *arterio venous oxygen difference* showed highly significant differences between patients with sinus rhythm and with atrial fibrillation, both at rest and during exercise Fig 20 shows that within both groups of descent rate the highest arterio-venous oxygen difference observed during exercise in patients with sinus rhythm was lower than the mean value of the corresponding patients with atrial fibrillation

The mean *brachial arterial pressure* was higher at rest in patients with atrial fibrillation, the difference was probably significant in the groups with the lower descent rate During exercise the pressures were of the same order in the two rhythms The *systemic vascular resistance*, however, was significantly higher in patients with atrial fibrillation both at rest and during exercise

The mean *pulmonary arterial pressure* was insignificantly higher in patients with atrial fibrillation Fig 21 illustrates that the individual pressures during exercise showed the same distribution in the two rhythms in patients having a descent rate of 15 mm/s or less In the groups with the higher descent rates three patients with atrial fibrillation had mean pressures of a magnitude (above 60 mm Hg) not seen in patients with sinus rhythm Nor did the *pulmonary arterial wedge pressures* show any significant differences between the two rhythms The calculated *pulmonary vascular resistance* was higher on the average in patients with atrial fibrillation but only in patients of the second group was a probably significant differ

matched for comparison of the hemodynamics. However, in the groups with the lower descent rate patients with sinus rhythm and with atrial fibrillation were comparable with regard to mitral valve areas estimated at operation and calculated by the Gorlin formula. Nor did the oxygen consumption at rest and during exercise differ significantly between the two rhythms. The mean heart rates at rest and during exercise were also virtually the same. When cardiac output and arterio-venous oxygen difference were compared significant differences were found between the two rhythms, the former was higher and the latter lower in the patients with sinus rhythm both at rest and during exercise as in SELZER's study (88). SELZER did not find any significant difference in pulmonary arterial pressure and in pulmonary vascular resistance between the patients with sinus rhythm and with atrial fibrillation. The average pulmonary arterial wedge pressure was lower in the latter patients but the difference was only probably significant. In the present series this pressure was on the average the same in the two rhythms.

WERKO (96) found that patients with atrial fibrillation had an almost complete loss of ability to regulate heart rate smoothly during exercise and considered this to be of great importance for their difficulty in maintaining an adequate blood flow. However at the work load used in the present study patients with sinus rhythm and with atrial fibrillation showed on the average the same heart rate during exercise. The insufficient increase in cardiac output during exercise in atrial fibrillation was manifested by the decrease of stroke volume in contrast to the slight increase in sinus rhythm.

The "myocardial factor" has been considered as one possible cause of the lower cardiac output in patients with atrial fibrillation: HARVEY and FERRER (51), FLEMING and WOOD (41). The larger heart volume in patients with atrial fibrillation in the present series would support this view as well as the higher average right atrial pressure in these patients. But the latter would also be caused by atrial fibrillation per se, thus REALE (77) found a significant decrease of the right atrial and right ventricular end diastolic pressures after conversion of atrial fibrillation to sinus rhythm.

A comparison between two patients with pure mitral stenosis, No. 92, belonging to clinical group III A and No. 119 of group III B, illustrates how the cardiac output in atrial fibrillation can be independent of the degree of stenosis. Both patients had a low cardiac output at rest, 2.6 and 2.0 l/min respectively, and during exercise, 4.6 and 5.3 l/min respectively. But the former patient had at operation a mitral valve area of 2.5 cm² while this was 1.1 cm² in the latter. This difference in valve area was manifested by the mean pulmonary arterial and pulmonary arterial wedge pressures during exercise; these were 26 and 14 mm Hg respectively in the former patient and 95 and 60 mm Hg respectively in the latter. The latter patient should be a candidate for surgery according to HARVEY and FERRER (51), while the former represented their group IV, considered as not suitable for surgery. The UCG was not able to separate these two patients sufficiently well: the descent rate was 16 mm/s in the former and 11 mm/s in the latter patient. However the valve areas calculated by the Gorlin formula were also small in both patients: 1.2 and 0.6 cm² respectively.

SUMMARY

Patients with a diastolic descent rate of 15 mm/s *or less in the UCG-tracing (first group)* were compared with those having a descent rate exceeding this

a mitral valve area estimated by the surgeon at 1 5 cm^2 or less were found in the group with a descent rate of 15 mm/s or less The mean value of the calculated mitral valve area in this group was 1 3 cm^2 which corresponds to the "critical narrowing of the mitral valve" according to DEXTER (17) On the other hand six patients in the group with the higher descent rate showed GORLIN areas of 1 5 cm^2 or less though the surgeon did not find any area less than 1 6 cm^2 in this group This indicates that the UCG-finding was more closely related to the valve area found at operation than the Gorlin area, this finding will be further studied in chapter VII

GRANATH (45) divided his material into patients with "tight" and "less tight" stenosis on the basis of the surgeon's estimate of the mitral ostium, an orifice of the latter size admitted the end phalanx of the surgeon's finger while an orifice of the former size did not The hemodynamic and some other findings in the two groups of patients were compared The cardiac output and the stroke volume at rest was significantly lower in the patients with more severe stenosis and sinus rhythm In the present series no such differences between the two groups of patients were found However, as in the present series, GRANATH (45) found a probably significant higher arterio venous oxygen difference in patients with "tight" stenosis the mean values in the two groups with sinus rhythm were virtually the same as in the present series He also found significantly higher pressures in the pulmonary circulation in the group with "tight" stenosis while the pulmonary and systemic vascular resistances did not differ significantly between the two groups

A significantly smaller stroke volume during exercise than at rest in the patients with sinus rhythm and "tight" stenosis was observed in GRANATH'S series (45), this is at variance with the present findings the mean values of the stroke volume increased slightly from rest to exercise in both groups of patients with sinus rhythm

The patients with atrial fibrillation were not so well separated into those with advanced and moderate stenosis by the descent-rate 15 mm/s The differences between the mean values of the two groups showed the same trend as in patients with sinus rhythm but none was statistically significant The distribution of the mitral valve areas estimated by the surgeon was almost similar in the two groups However, five patients with very tight stenosis, 0 9–1 1 cm^2, were all found in the group with the lower descent rate A comparison between fig 16 and 17 reveals the great difference between surgically estimated valve areas and areas calculated by the Gorlin formula The poor correlation between these two areas as well as the influence of the changes in the anterior mitral leaflet upon the correlation between descent rate and valve areas will be discussed in chapter VI and VII

The hemodynamics in cases of mitral stenosis with sinus rhythm and with atrial fibrillation has been compared by several authors, for a review of this subject reference should be made to WERKO (96) The comparison has been made either between different groups of patients matched according to pulmonary arterial pressure VARNAUSKAS et al (91) and calculated mitral valve area, SELZER (88) or between patients before and after conversion of atrial fibrillation by quinidine BROCH and MULLER (13) or by electric countershock e g REALE (77) These authors found higher cardiac output in patients with sinus rhythm

In the present study patients with the two rhythms were not intentionally

CHAPTER VI

THE RELATIONSHIP BETWEEN UCG FINDINGS AND SURGICAL FINDINGS

In hitherto published studies of UCG in mitral stenosis the descent rate of the UCG tracing during diastole has mostly been related to a *rough estimate of the* size of the mitral orifice at operation In the present study the mitral valve area was measured in square centimeters with a method showing a good reproducibility (see *chapter II*) Thus it was possible to perform a statistical evaluation of the correlation between the diastolic descent rate and the valve area

The maximal amplitude of the UCG tracing, i e the distance between the highest and the lowest point of the tracing is considered to represent the maximal excursion of the anterior mitral leaflet in a plane perpendicular to the ultrasonic beam thus it could be of value in estimating the mobility of the leaflet before operation The mobility and the degree of calcification were recorded during operation and related *to the maximal amplitude*

THE CORRELATION BETWEEN DESCENT RATE AND MITRAL VALVE AREA

The correlation between the descent rate and the mitral valve area was statistically highly significant when calculated for the whole material table 15 fig 24 This figure also shows that patients with an UCG tracing of low maximal amplitude (15 mm or less) showed a poor correlation between descent rate and valve area All but two of these patients had descent rates between 7 and 14 mm/s the corresponding valve areas ranged between 0 9 and 2.5 cm² If these patients with low maximal amplitude were excluded the coefficient of correlation was 0 64 ($p<0\ 001$) for the relation between descent rate and valve area

The best correlation between the UCG finding and mitral valve area was found in the patients with sinus rhythm

Table 1 *Diastolic descent rate mm s (x) related to mitral valve area cm² (y) Correlation and regression*

	n	$\bar{x}$	$\bar{y}$	r	p	Regr equation	$S_{y\cdot x}$
All patients	1	16 3	1 6	0 51	< 0 001	y 0 051x − 0 93	± 0 40
Patients with maximal amplitude 15 mm							
Sinus rhythm and atrial fibrillation	59	1 1	1 76	0 64	0 001	y 0 067x + 0 62	± 0 37
Sinus rhythm	34	1 9	1 84	0 72	0 001	y 0 071x − 0 57	± 0 35
Atrial fibrillation	25	16 0	1 66	0 39	0 1−0 05	y − 0 019x + 1 17	± 0 40

figure (second group) The comparison was performed with respect to some clinical data, operative findings and hemodynamics Patients with sinus rhythm and with atrial fibrillation in the respective groups of descent-rate were compared separately and in conjunction with each other

1 *Sinus rhythm* 16 patients in the first group were compared with 23 patients in the second group The mitral valve areas estimated at operation and by the Gorlin formula were significantly smaller in the first group, in which the surgically estimated area was less than 1 5 cm² in about 50 per cent of the patients The pulmonary arterial and pulmonary arterial wedge pressures were significantly higher in the first group at rest and during exercise The arterio venous oxygen difference was probably significantly higher in this group

2 *Atrial fibrillation* 15 patients in the first group were compared with 17 patients in the second group The mean differences between the groups showed the same trend as in sinus rhythm but none was statistically significant

3 *Sinus rhythm compared with atrial fibrillation* The groups with the lower descent rate were comparable with regard to UCG findings and mitral valve areas The patients with atrial fibrillation showed significantly larger heart volume, lower cardiac output and higher arterio venous oxygen difference at rest and during exercise The right atrial pressure at rest and the systemic vascular resistance were significantly higher in atrial fibrillation

CHAPTER VI

THE RELATIONSHIP BETWEEN UCG-FINDINGS AND SURGICAL FINDINGS

In hitherto published studies of UCG *in mitral stenosis* the descent rate of the UCG tracing during diastole has mostly been related to a rough estimate of the size of the *mitral orifice at operation*. In the present study the mitral valve area was measured in square centimeters with a method showing a good reproducibility (see chapter II). Thus it was possible to perform a statistical evaluation *of the correlation* between the diastolic descent rate and the valve area.

The *maximal* amplitude of the UCG tracing, *i.e.* the distance between the highest and the lowest point of the tracing, is considered to represent the maximal excursion of the anterior mitral leaflet in a plane perpendicular to the ultrasonic beam; thus it could be of value in estimating the mobility of the leaflet before operation. The mobility and the degree of calcification were recorded during operation and related *to the maximal amplitude*.

THE CORRELATION BETWEEN DESCENT RATE AND MITRAL VALVE AREA

The correlation between the descent rate and the mitral valve area was statistically highly significant when calculated for the whole material (table 15, fig. 24). This figure also shows that patients with an UCG tracing of low maximal amplitude (15 mm or less) showed a poor correlation *between* descent rate and valve area. All but two of these patients had descent rates between 7 and 14 mm/s; the corresponding valve areas ranged between 0.9 and 2.5 cm². If these patients with low maximal amplitude were excluded, the coefficient of correlation was 0.64 ($p<0.001$) for the relation between descent rate and valve area.

The best correlation between the UCG-finding and mitral valve area was *found in* the patients with sinus rhythm

Table 15. *Diastolic descent rate mm/s (x) related to mitral valve area cm² (y). Correlation and regression*

	n	$\bar{x}$	$\bar{y}$	r	P r	Regr. equation	S y . x
All patients	1	16 3	1 7b	0 51	0 001	y 0 051x + 0 93	± 0 40
Patients with maximal amplitude > 15 mm							
Sinus rhythm and atrial fibrillation	59	1 1	1 6	0 64	0 001	y 0 06 x + 0 62	± 0 3
Sinus rhythm	34	1 9	1 84	0 2	0 001	y − 0 0 1x + 0 57	± 0 35
Atrial fibrillation	25	16 0	1 66	0 39	0 1—0 05	y 0 019x − 1 17	± 0 40

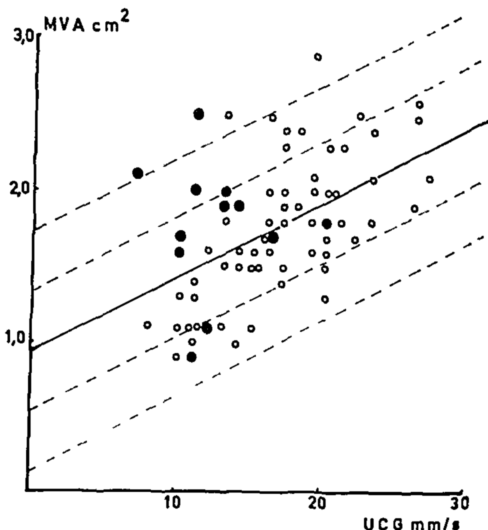

Fig 24 The relation of the diastolic descent rate to the mitral valve area estimated at operation in the whole material Large filled circles represent patients with maximal amplitude $\leq$ 15 mm Regression line $\pm$ Sy x and 2 Sy x

and a maximal amplitude of more than 15 mm, table 15, fig 25

The correlation was less good, not significant, for the corresponding patients with atrial fibrillation, table 15, fig 26 The low coefficient of correlation was partly due to the patients Nos 92 and 120, who, though the maximal amplitude was more than 20 mm, showed rates of 16 and 13 mm/s at areas of 2 5 cm², without these patients the correlation was significant even in patients with atrial fibrillation ($r = 0\ 59$ $p < 0\ 01$)

In the present series there was a wide range of the body surface area, 1 43–2 24 m² ARAUJO and LUKAS (3) considered that the effect of a stenotic mitral orifice of similar size in different sized individuals was obviously different they related the mitral valve area to the body surface area and expressed the former as a 'mitral valve index When such an "index was used in the present series the correlation to the descent rate was of the same order as when the "uncorrected" area was used in patients with sinus rhythm thus the coefficient

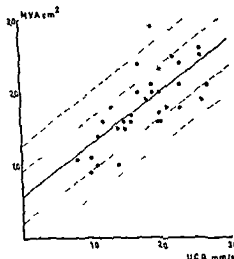

Fig 25 *The relation of the diastolic descent rate to the mitral valve area estimated at operation in patients with sinus rhythm and maximal amplitude > 15 mm Regression line ± S y x and 2 S y x*

of correlation for the patients with this rhythm and a maximal amplitude more than 15 mm was 0 73 ($p < 0\ 001$) However the correlation became slightly improved and probably significant in the corresponding patients with atrial fibrillation ($r = 0\ 47$, $p < 0\ 05$)

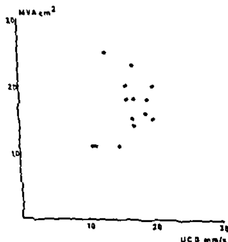

Fig 26 *The relation of the diastolic descent rate to the mitral valve area estimated at operation in patients with atrial fibrillation and maximal amplitude > 15 mm*

The influence of mitral regurgitation estimated by the surgeon upon the correlation between descent rate and valve area was also studied When it was calculated for 52 patients with no or (+) degree of regurgitation irrespective of rhythm and maximal amplitude, a coefficient of correlation of 0 48 was found ($p < 0\ 001$) for 19 patients with (++) and (+++) regurgitation it was 0 64 ($p < 0\ 001$)

THE RELATION OF MAXIMAL AMPLITUDE TO AGE, MOBILITY OF THE ANTERIOR MITRAL LEAFLET, CALCIFICATIONS AND MITRAL INSUFFICIENCY

The mean value of the maximal amplitude in the present series was 20 0 mm

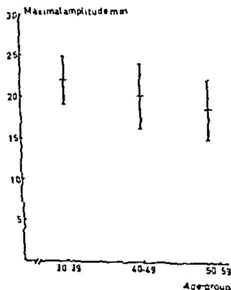

Fig 27 *The relation of the maximal amplitude to age groups Mean values ± S D*

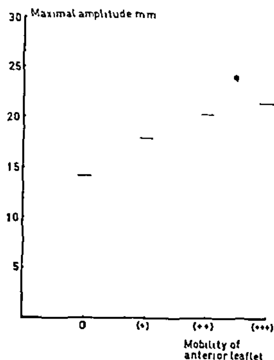

Fig 28 *The relation of the maximal amplitude to the mobility of the anterior mitral leaflet Horisontal lines represent mean values*

No significant correlation was found between the amplitude and the *age* of the patients ($r = -0\ 21$) However, when the material was divided into age groups (the groups 20—29 years with one patient and 60—69 with three patients were omitted), the mean value of the amplitude decreased with increasing age, fig 27 The difference between the mean values of the groups 30—39 and 50—59 years was statistically significant ($p < 0\ 01$) Twelve patients had an amplitude of 15 mm or less, four of these were found in the age group 40—49 years, the remaining were more than 50 years of age, no one was younger than 40

The relation of the maximal amplitude to the *mobility of the anterior mitral leaflet* is shown in fig 28 The mean value of the amplitude increased with increasing mobility of the leaflet A highly significant correlation between amplitude and mobility was shown by analysis of variance (table 16)

Calcifications of the mitral valve were found at operation in twenty six patients, ten women and sixteen men In fourteen patients the calcifications were of the most advanced type, two of these were women and twelve men All patients with the most advanced calcifications were more than 40 years of age, eight were aged 40—49, the remaining were over 50

Calcifications had been diagnosed by cinefluorography in all the patients where they were of degree (+++) or (++) but only in one of the seven patients with calcifications of the slightest degree

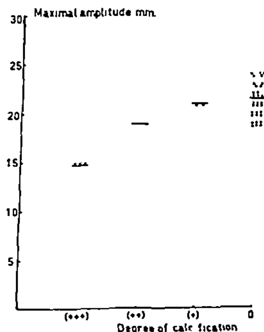

Fig 29 *The relation of the maximal amplitude to the degree of calcification of the mitral valve Horisontal lines represent mean values*

Fig 29 shows the distribution of the maximal amplitude in relation to the different degrees of calcification The mean value of the amplitude decreased with an increasing degree of calcification By analysis of variance a highly

Table 16 *The relation of maximal amplitude (mm) to mobility of anterior leaflet and to calcifications*
(Analysis of variance)

	Degrees of freedom	Variances	F test	P
Mobility				
Between groups	3	101.0	$F_{3,67} = 8.7$	< 0.001
Within groups	67	11.6		
Calcifications				
Between groups	3	169.5	$F_{3,67} = 19.9$	< 0.001
Within groups	67	8.5		

Table 17 *Maximal amplitude and degree of mitral insufficiency estimated by the surgeon*

Degree of mitral insufficiency	n	Max ampl (mm) Mean ± S.E.	Diff ± S.E. of the mean diff	P
0 and (+)	52	20.9 ± 0.50	3.4 ± 1.0	< 0.01
(+ +) and (+ + +)	19	17.5 ± 0.86		

significant correlation between calcification and amplitude was shown to exist (table 16). The statistical significance was entirely due to the group with the most advanced calcification.

The relation between the maximal amplitude and the degree of *mitral insufficiency* estimated by the surgeon was also studied (table 17). The mean value of the amplitude was significantly higher in patients with no or the slightest degree of regurgitation than in those with (+) and (+ + +) regurgitation.

In fourteen of the forty one patients with pure stenosis at the initial palpation a regurgitant jet could be felt after dilatation of the valve. The mean value of the maximal amplitude in these fourteen patients before operation did not differ significantly from that of the patients where no regurgitation was produced.

DISCUSSION

The origin of the UCG tracing in relation to the movements of the normal and stenotic mitral valve

The normal mitral valve consists of a larger anterior or septal leaflet about 2.2 cm in length from base to apex and a smaller posterior or mural leaflet about 1.3 cm in length. RUSTED et al (81), DU PLESSIS and MARCHAND (75). These two major leaflets are normally joined by the two commissures or junctional areas about 0.8 cm in depth. RUSTED et al (81). Thus the mitral leaflets form a continuous veil or "sleeve" BAILEY et al (6) attached to the mitral ring and hanging down in the left ventricle.

Fig. 30 a shows the UCG tracing of the anterior mitral leaflet related to the movements of this leaflet in a *normal subject*. At the beginning of diastole

when the ventricular pressure falls below the atrial pressure, the "sleeve" opens and the anterior leaflet with its free margin moves forward When this movement is completed the leaflet is stretched, as shown by PUFF et al (76) in a cineangiocardiographic study in a sheep In this position it is nearest the thoracic wall and the exploring crystal, the UCG-curve has reached its highest point (position 1)

Immediately after this the UCG curve shows a rapid downward movement to point 2, the rate of descent being 85—150 mm/s in subjects without mitral stenosis, EDLER and GUSTAFSON (29) This must correspond to a movement of the anterior leaflet in a dorsal direction in connection with the early rapid ventricular filling phase to a position intermediate between the fully opened and closed one The vertical distance between position 1 and 2 averaged 17 mm in 86 normal subjects examined by EDLER (26)

During atrial systole the flow of blood through the mitral valve is accelerated and there is again a forward movement of the anterior leaflet which is reflected in the UCG-curve as an upward movement of short duration When the ventricular pressure exceeds that in the atrium in the beginning of ventricular systole there is a sudden change of the direction of the blood stream The walls of the "sleeve collapse and the anterior leaflet moves in a dorsal direction and "balloons" into the atrium At this position the leaflet is most remote from the thoracic wall at the same time the UCG curve has reached its lowest point (position 3 in fig 30 a)

The distance between the lowest and the highest point of the UCG tracing that is the distance the anterior leaflet moves from the closed to the fully opened position, normally averages 24 mm (range 19—30 mm) according to EFFERT (33) EDLER (26) found the same value in 86 normal subjects when he used the photographic registration method, the same author found a mean value of 27 mm (range 20—33 mm) with the direct writing method in 53 normal subjects (28)

The amplitude of the excursions of the normal anterior mitral leaflet has not been studied in man by any other method The movements of the mitral valve have also been studied by angio cardiography but with this method the normal leaflets are seen only in systole, KJELLBERG et al (62), ROSS and CRILEY (80) PUFF et al (76) studied the movements of the mitral leaflets in a sheep by combined left atrial and left ventricular cineangiocardiography and found a movement pattern of the anteri or leaflet which supports the pre ent description derived from the UCG curve

RUSTED et al (82) studied the *anatomical basis for mitral stenosis* in 70 hearts and classified the changes into four groups namely, commissural, cuspal chordal and combined types In 53 hearts the commissural changes were important and in 22 of these cases the changes were restricted to the commissures In this type of mitral stenosis described as mitral stenosis with minimal valvitis by BROCK (80) the anterior leaflet is still thin and has retained its normal mobility even if the margin may be thickened

Fig 30 b illustrates the UCG tracing in relation to the movements of the anterior leaflet in the type of mitral stenosis where the anterior leaflet has retained its mobility In early dia tole the anterior leaflet moves downward and forwards into the left ventricle (point 1) As the free edge of the leaflet i partially fixed to the shorter po terior leaflet by the commissural changes it cannot move forward in the normal way This results in a bulging of the anterior leaflet into the left ventricular outflow tract a phenomenon which was initially

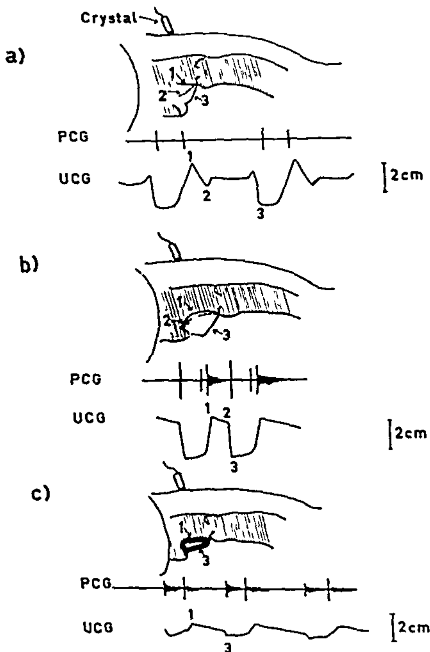

Fig. 30. The relation between the movements of the anterior mitral leaflet and the UCG-tracing in a) normal mitral valve, b) mitral stenosis with good mobility of the anterior mitral leaflet and c) mitral stenosis with restricted mobility of the anterior leaflet. The anatomical pictures in b) and c) are drawings from left ventricular angiocardiographies performed in the patients whose UCG-tracings are illustrated.

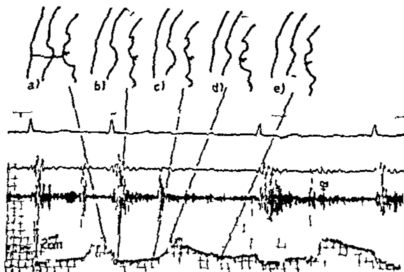

Fig 31 Above drawings from a left ventricular cine angiocardiography (lateral projection) in a patient with mitral stenosis (case No 146 of the present series) below the UCG tracing of the same patient The individual pictures of the cine angiocardiography were related to the UCG tracing by means of the exposure markings on the electrocardiogram

The dotted line represents the ultra sound beam the arrows indicates the *anterior mitral* leaflet a) shows the anterior leaflet in the open position at the end of a short *diastole b) the* valve is closed and the UCG tracing *has reached* its lowest point In c) the ballooning of the leaflet against the atrium is less in late systole the UCG tracing has begun to rise d) the leaflet *in the* open position in *early* diastole the UCG tracing has reached its highest point after a steep *ascent e) the leaflet has* moved against the atrium in the middle of a *long* diastole and the UCG tracing has descended to a horisontal level

described by ARVIDSSON (4) as "ballooning" or "dome shape" of the mitral *leaflets*

In mitral stenosis of a significant degree there is no early rapid filling of the left ventricle but a slow gradual emptying of the left atrial blood through the narrowed mitral orifice This is reflected in the left atrial pulse pressure tracing as a slow "y descent" and in the left atrial volume curve constructed by ARVIDSSON (4) as an only small decrease in diastolic volume before the atrial contraction In the UCG curve this corresponds to a slow downward movement of the curve during diastole (from point 1 to point 2 in fig 30 b), instead of the early rapid diastolic descent in cases without mitral stenosis

If the mitral stenosis is mainly caused by commissural fusion of otherwise normal leaflets it can be assumed that the narrower the mitral orifice is, the more slowly the mitral funnel will empty itself the more slowly the anterior leaflet will move in a dorsal direction and the UCG curve downwards The diastolic descent rate of the UCG tracing will thus be primarily dependent on the size of the mitral orifice

In ventricular systole the anterior leaflet "balloons" towards the atrium in the normal way in this type of mitral stenosis, thus the amplitude of the excursions of the anterior leaflet between its fully opened and closed position is not reduced (the distance between point 1 and 3 in fig 30 b)

The relation between the movements of the anterior mitral leaflet and the UCG curve is further illustrated by fig 31 which shows the UCG curve related

to drawings from a cineangiocardio graphy in a patient with mitral steno is

In the other anatomical types of mitral steno is the changes are not confined to the commissures and to the margins of the cusps In the cu pal type the leaflets are involved to the greatest extent they are thickened stiff and rigid often with calcifications In the chordal type the changes mainly involve the chordae which are thickened short ened and frequently fu ed In the com bined types the commi sures the cu ps and the chordae can all be involved to varying extent

In the e types of mitral steno is the mobility of the anterior leaflet i restricted Fig 30 c illustrates the move ments of the anterior leaflet and the corre ponding UCG tracing In dia tole the leaflet cannot move forwards into the ventricle in the normal way nor does it balloon into the atrium during ventricular systole the amplitude be tween the open and clo ed po ition of the leaflet is reduced The slow descent of the UCG tracing during diastole may be mainly cau ed by the changes in the leaflets and chordae not being primarily related to the area of the mitral orifice

When the mitral stenosis is cau ed by commis ural fu ion of thin and mobile leaflets it can be a sumed that the mitral valve area e timated by the surgeon fairly well repre ents the degree of functional stenosi But when the tenosis is mainly due to rigidity of the leaflets the functional effect is often more advanced than indicated by the mitral valve area obtained at operation As pointed out by LOGAN et al (68) and by MOUNSEY (73) the leaflets in these cases constitute an ob truction to flow though they can be separated by the surgeon s finger

The diastolic de cent rate related to the mitral valve area In earlier inve tigations relating the rate of diastolic de cent of the UCG tracing to the degree of mitral stenosi , the latter was expres ed as the degree of admittance of the mitral orifice for the surgeon s finger Because of this rough e timate of the mitral valve area a stati tical evaluation of the correlation between the degree of stenosis and the descent rate could not be performed Nor did the early reports give any other information about the condi tion of the mitral valve, partly because the UCG curve was pre umed to ari e from movements of the anterior wall of the left atrium until EDLER et al (30 31) found that the anterior mitral leaflet was the echo giving structure In a recent report JOYNER et al (59) *mentioned* that the descent rate corre lated well with the size of the orifice "regardle s of whether the valvular sub tance was thin or thickened the re ults of the present study are at variance with this statement

Table 18 summarizes the re ults of earlier investigations of the relation between the UCG-finding and the degree of mitral stenosis The angle values used by EDLER and GUSTAFSON (29) and GASSLER and SAMLERT (48) have been transferred into rate in mm s as proposed by EFFERT (33) EFFERT (33) and EFFERT et al (34) u ed the clinical picture wedged pressures or left auricular pres ures the phonocardiogram and the operative findings to evaluate the degree of mitral stenosis The exact number of operated patients was not given

As is evident from the table the find ings of EDLER and GUSTAFSON agreed well with tho e of EFFERT GASSLER and SAMLERT gave the mitral valve area in a sliding scale of square centimeters corre ponding to different objects as for in tance grain of rice or plum stone" The values of descent rate in their patients were higher than tho e found by EDLER and EFFERT at corre ponding valve areas

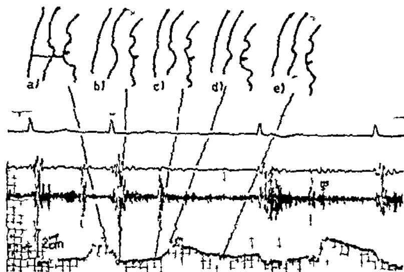

Fig 31 Above drawings from a left ventricular cine angiocardiography (lateral projection) in a patient with mitral stenosis (case No 146 of the present series) below the UCG-tracing of the same patient The individual pictures of the cine angiocardiography were related to the UCG tracing by means of the exposure markings on the electro cardiogram

The dotted line represents the ultrasound beam the arrows indicates the anterior mitral leaflet a) shows *the anterior leaflet in the open* position at the end of a short diastole b) the valve is closed and the UCG tracing has reached its lowest point In c) the "ballooning" of the leaflet against the atrium is less in late systole the UCG tracing has begun to rise d) the leaflet in the open position in early diastole the UCG tracing has reached its highest point after a steep ascent e) the leaflet has moved against the *atrium in the* middle of a long diastole and the UCG tracing has descended to a horizontal level

described by ARVIDSSON (4) as "ballooning" or 'dome shape' of the mitral leaflets

In mitral stenosis of a significant degree there is no early rapid filling of *the left* ventricle but a slow gradual emptying of the left atrial blood through the narrowed mitral orifice This is reflected in the left atrial pulse pressure tracing as a slow "y descent" and in the left atrial volume curve constructed by ARVIDSSON (4) as an only small decrease in diastolic volume before the atrial contraction In the UCG curve this corresponds to a slow downward movement of the curve during diastole (from point 1 to point 2 in fig 30 b), instead of the early rapid diastolic descent in cases without mitral stenosis

If the mitral stenosis is mainly caused by commissural fusion of otherwise normal leaflets it can be assumed that the narrower the mitral orifice is, the more slowly the mitral funnel will empty itself the more slowly the anterior leaflet will move in a dorsal direction and the UCG curve downwards The diastolic descent rate of the UCG tracing will thus be primarily dependent on the size of the mitral orifice

In ventricular systole the anterior leaflet "balloons" towards the atrium in the normal way in this type of mitral stenosis, thus the amplitude of the excursions of the anterior leaflet between its fully opened and closed position is not reduced (the distance between point 1 and 3 in fig 30 b)

The relation between the movements of the anterior mitral leaflet and the UCG curve is further illustrated by fig 31 which shows the UCG curve related

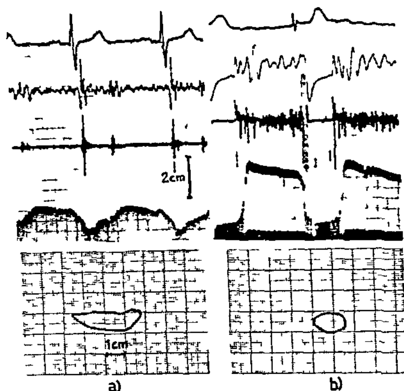

Fig 32 *UCG-tracing and the surgeon's estimate of the mitral valve area in case No 75 and 119 For legend see text*

a maximal amplitude of 15 mm or less Ten of these patients had a descent rate of 15 mm/s or less only two of these had a valve area of 1.5 cm or less On the other hand of the twenty patients having a maximal amplitude exceeding 15 mm and a descent rate of 15 mm/s or less fifteen or 75 % had a valve area of 1.5 cm² or less

EFFERT (33) also mentioned that the descent rate was not a reliable measure of the degree of mitral stenosis in patients with a *maximal* amplitude less than 15 mm He thought that this could be due to changes in the left atrial wall, which at that time was considered to be the echo giving structure

The valvular changes in the patients having a low maximal amplitude could represent the changes illustrated in fig 30 c in which it was supposed that the slow diastolic descent was mainly caused by changes in the leaflets themselves and not primarily by the constriction of the mitral orifice as shown in fig 30 b

To illustrate this statement the UCG tracings and the mitral valve areas estimated by the surgeon of two patients No 75 and 119 are shown in fig 32

In patient No 75 (fig 32 a) the mobility of the anterior leaflet was only slight and gross calcifications in both leaflets were found at the operation, the mitral valve area was 2.1 cm² and the intercommissural diameter 35 mm which

Table 18

Authors	*Degree of mitral stenosis*	*Descent rate of UCG (mm/s)*	
EDLER and GUSTAFSON 1957	½ fingertip	6 (3—8)*	
40 cases	<1 fingertip	9 (7—13)	
	1 fingertip	13 (9—17)	
	1 finger	17 (10—21)	
		(I)	(II)
EFFERT 1959 (I) 432 cases	Extreme degree of mitral stenosis	<10	<10
EFFERT et al 1964 (II) 2156 cases	High grade mitral stenosis (Finger tips size)	10—20	10—25
	Borderline cases	20—30	26—35
	Mitral stenosis functionally insignificant		>35
GASSLER and SAMLERT 1958 28 cases	0.4 cm²	11	
	0.6 cm²	15	
	1.0 cm²	21	
	1.5 cm²	23	
	3.0 cm²	23—28	
	4.5 cm²	28—34	

* Mean values of descent rate range within brackets

In a recent report BRAUN and SCHMITT (12) briefly mentioned that an angle value of 20° (descent rate 18 mm/s) corresponded to a mitral valve area of 1—1.2 cm² according to their experience.

Table 18 shows that the range of the UCG values was often rather wide, especially in a valve area of about one finger in size. JOYNER et al (60) plotted the velocity of motion in the UCG tracing against the mitral valve area expressed in fingers. The size of the ostium was determined during surgery or necropsy in the 60 patients. About 20 of the patients had a mitral ostium with the size of one finger, the figures for velocity in these ranged between approximately 3 and 26 mm/s.

SEGAL et al (85) found descent rates between 10 and 30 mm/s in patients with stenosis one finger in size at operation. When the orifice admitted 1 ½ finger the descent rate ranged between 26 and 49 mm/s; the values of descent rate in their study are higher than those reported by others.

In the present series the correlation between the rate of diastolic descent and the mitral valve area estimated at operation was statistically highly significant. However the scatter of the mitral valve area in relation to the descent rate was great: in twelve patients having

type of steno is there is a definite indication for open heart surgery, ELLIS and ADLER (40), JOHNSON et al (57), KAY and ZIMMERMAN (61), LITWAK et al (67)

MORROW et al (72) found that "the mobility of valve leaflets proved to be the best common denominator by which to distinguish the various types of stenotic lesions" They divided their material of 33 patients into 3 types according to operative findings Type I fusion of commissures, both leaflets retaining normal mobility, Type II fusion of commissures anterior leaflet mobile but posterior rigid and fixed Type III fusion of commissures, both leaflets completely immobile At the postoperative evaluation they found a normal left atrial pressure in 11 of 12 patients with type I valve it remained high in 6 of 7 patients with type III valve while 8 of 14 patients with type II valve had a normal left atrial pressure LITWAK et al (67) divided their material into similar groups and concluded that only in the first group could closed operation accomplish anatomic and hemodynamic restoration of mitral valve function

The mobility and the condition of the anterior leaflet is of greater importance for the mitral valve function than that of the posterior leaflet BAILEY et al (6), AMADOR et al (2) The latter is usually fibrosed and rigid in mitral stenosis, being converted into ' an arcuate cornified shelf BAILEY et al (6) because the rheumatic inflammation and subsequent fibrosis involves a relatively larger portion of the shorter posterior leaflet RUSTED et al (82) DU PLESSIS and MARCHAND (75)

In the present material the mobility of the posterior leaflet was estimated by the surgeon as 'good in only 4 cases in 26 cases a slight mobility of a narrow zone of the posterior leaflet was found in 40 cases it was immobile and in one case there was no information about this leaflet

The mobility of the mitral valve is often difficult to assess before operation The physical findings have been widely used for this purpose a loud first sound and a prominent opening snap being considered as signs of a thin and pliant anterior leaflet e g WOOD (97), SELLORS et al (87), MORROW et al (72) LOGAN and TURNER (69) partly agreed to this but they had seen so many exceptions to this statement that they considered it impossible to make a reliable prognosis in the individual case KAY et al (61), advocating open heart surgery in mitral stenosis found the preoperative differentiation between the "simple' and ' complicated valves impossible

Angiocardiography has been used to study the mobility of the mitral valve Thus KJELLBERG et al (62) found that in 30 cases of mitral stenosis the mean mobility of the anterior leaflet, measured as the greatest excursion between ventricular systole and diastole was 12 mm, range 4 to 29 mm In 10 cases the excursion of the anterior leaflet was less than 9 mm in 4 of these combined mitral stenosis and incompetence was found at operation 4 had calcifications of the leaflets and in one case the orifice consisted of a fibrous funnel

KJELLBERG et al (62) also measured the cyclic excursions of the atrioventricular plane This movement in five cases of pure mitral stenosis amounted to a mean of 3 mm

BROLIN et al (15) used cineangiocardiography with left atrial injection in 11 cases of mitral stenosis to study the mobility of the mitral leaflets The amplitude of excursion of the anterior leaflet in one case was 20 mm at operation the changes in leaflets and chordae were slight Another case with an amplitude of 10 mm showed at operation advanced changes in leaflets and chordae with calcifications The pattern of movement of the anterior leaflet during diastole found by the e

is within the normal range found by Rusted et al (81) Thus the mitral stenosis, which was hemodynamically significant, was probably caused by the stiff leaflets In the UCG-tracing the maximal amplitude was 13 mm and the rate of diastolic descent 7 mm/s

In patient No 119 (fig 32 b) the mobility of the anterior leaflet was estimated as almost normal and only questionable small calcifications in the anterior commissure were found by the surgeon The mitral valve area was 1 1 cm² with an intercommissural diameter of 15 mm In this patient the stenosis, which functionally was one of the most advanced in the present series, was mainly caused by commissural fusion of the slightly changed leaflets The maximal amplitude averaged 28 mm and the descent rate 11 mm/s The correlation between descent rate and the anatomical mitral valve area was good in this patient in contrast to the former one

No separation of the materials into *patients with sinus rhythm and with atrial fibrillation* has been made in earlier investigations of the relationship between UCG findings and the degree of mitral stenosis In the present series the correlation between the descent rate and the mitral valve area was stronger for the patients with sinus rhythm than for those with atrial fibrillation

The cause of this difference is obscure It can hardly be explained by an influence of the irregular rhythm per se on the descent rate in atrial fibrillation The variation in the measured values is not greater in atrial fibrillation than in sinus rhythm, nor is there any correlation between the descent rate and the length of diastole as shown by Effert (33) and the present author

One possible reason would be a higher frequency of mitral stenosis caused by leaflet changes in the patients with atrial fibrillation But if the patients with a low maximal amplitude were omitted the difference between the two rhythm persisted Nor was there any significant difference between the mean values of maximal amplitude in patients with sinus rhythm and with atrial fibrillation

As pointed out previously the weak correlation was partly due to patients Nos 92 and 120 who showed slow diastolic descent rates with large mitral valve areas in spite of normal maximal amplitude and freely movable anterior leaflets at operation No technical errors in the recordings of the UCG tracing or operative findings were found which could explain this discrepancy

The existence of a certain degree of *mitral insufficiency* did not adversely affect the correlation between the descent rate and the mitral valve area in this series of patients with predominant mitral stenosis Thus the descent rate reflected the degree of stenosis irrespective of a certain element of incompetence in contrast to the findings of Segal et al (85), who reported higher descent rates when a dominant mitral stenosis was associated with mitral regurgitation

The relation of the maximal amplitude of the UCG tracing to mobility and calcifications of the mitral valve The importance of the condition of the leaflets for the result of mitral commissurotomy has been stressed by many authors, e g Baden (5), Brock (14) Ellis et al (39), Litwak et al (67) Morrow et al (72), Sellors et al (87) and Wood (97)

The best results are to be expected in mitral stenosis caused by commissural fusion of thin and supple leaflets At the other extreme is the type of stenosis where the leaflets are thickened and leathery, often with calcifications Even if commissural fusion exists also here and can be treated, there will still be a functional stenosis often with an element of incompetence In the latter

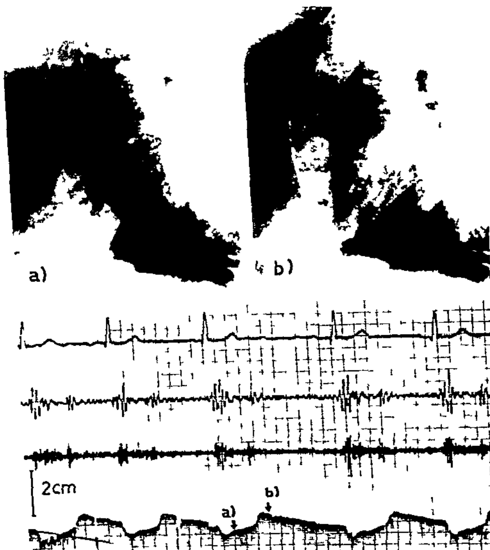

Fig 34 Shown above is a left ventricular angio-cardiography (lateral projection) in a male aged 54 with mitral stenosis and insufficiency (case No 150 of the present series) below the LCG tracing of the same patient Same symbols as in fig 33

The roentgenologist estimated the mobility of the anterior mitral leaflet as slight the largest distance between the closed and open position was estimated as about 10 mm which agrees with the maximal amplitude of the LCG-tracing

Surgical findings the mobility of the anterior leaflet was estimated as 0 the calcifications as (+ + +) and the mitral valve area as 2 0 cm²

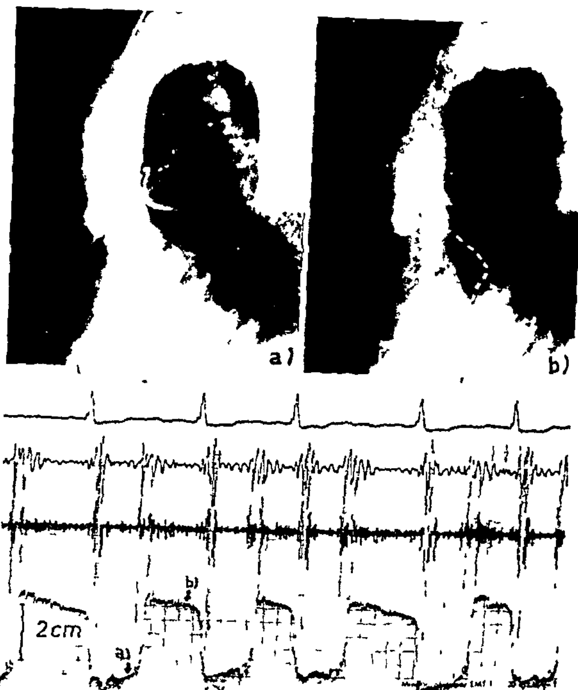

Fig 33 Shown above is a thoracic aortography with regurgitation of contrast medium to the left ventricle (lateral projection) in a woman aged 57 with mitral stenosis and aortic insufficiency below the UCG tracing of the same patient The anterior mitral leaflet is indicated by arrows in its closed (a) and open position (b) The dotted line in b) represents the position of the leaflet in a)

The points on the UCG tracing corresponding to the X ray exposures are indicated

The roentgenologist estimated the mobility of the anterior leaflet as good the largest distance between the closed and open position of the leaflet was measured as about 25 mm which agrees with the maximal amplitude of the UCG tracing

Surgical findings the mobility of the anterior leaflet was estimated as (++) no calcifications were found and the mitral valve area was estimated as 1 3 cm²

of 15 mm, the same value of the excursion of the anterior leaflet was found on left ventricular angiocardiography. An other patient with good mobility and an amplitude of 16 mm had advanced calcifications of *both leaflets*. In the two other groups with slight and moderate mobility the pattern of amplitude was more mixed which is not surprising having regard to the less well defined degree of mobility in these groups.

The maximal amplitude of the UCG tracing was also significantly correlated to the degree of calcification estimated by the surgeon, a correlation which was due to the group with the most advanced calcification. In this group 9 of 14 patients had an amplitude of 15 mm or less, in only one patient was it 20 mm.

The leaflets with no and slight mobility also showed the most advanced type of calcification in 47 %. *But in one of* the patients with an immobile anterior leaflet and very low amplitude 13 mm no calcifications were found at operation. Three of the five patients with calcifications designated as (++) at operation all demonstrated by cinefluorography had an amplitude of 20 mm or more and moderate or good mobility of the anterior leaflet at operation. This corresponds to the findings of MICHELL (71) that in some instances with calcium deposition the leaflets are relatively supple and non shrunken. JOYNER et al (59) also reported that three of their patients with dense calcification by fluoroscopy, but thin echoes with good excursion were found to have annulus calcifications with pliable leaflets.

JOYNER et al (60) stated that they did not have adequate experience to determine what UCG-pattern was to be expected from a stenotic immobile mitral valve with a fixed opening permitting significant regurgitation. In the present series the maximal amplitude was significantly higher in the group of patients with no or the slightest degree of incompetence than in those with regurgitation still palpable 2—3 fingers from the mitral ostium. This would be consistent with the observation that stenotic mitral valves with rigid and calcified leaflets are often also incompetent to a certain degree, e g BROCK (14), KJELLBERG et al (62) and WOOD (97). The anterior leaflet was immobile or showed an only slight mobility in 47 % of the patients with regurgitation palpable more than two fingers from the ostium, in 68 % of these patients some degree of calcification was found. A regurgitant jet was palpated by the surgeon in nine of the twelve patients with a maximal amplitude of 15 mm or less though in three patients it was of the slightest degree.

Because of the selection of the material no patient with dominant or pure mitral incompetence was included in the present study. This type of mitral valvular disease most often shows a normal or even increased maximal amplitude EDLER (28).

SUMMARY

Two components of the UCG-tracing the diastolic descent rate and the maximal amplitude were correlated to the surgical findings.

1. For the whole series of 71 patients a highly significant correlation was found between descent rate and mitral valve area. The scatter of valve areas in relation to descent rate was great in patients with a maximal amplitude of 15 mm or less and the surgically measured area was often larger than predicted by the descent rate in these patients.

2. When the material was divided in sinus rhythm and atrial fibrillation the best correlation between descent rate and valve area was found in patients with sinus rhythm and a maximal amplitude exceeding 15 mm. The corre

authors is also of interest because it closely mimics the UCG curve in mitral stenosis REES et al (78) also studied the mobility of the mitral cusps by cineangiocardiography and their findings agreed well with the surgeon's estimate in most cases

Calcifications are often found when the anterior leaflet is severely sclerosed and immobile Thus the demonstration of calcifications by different roentgen techniques such as tomography, e g LINKO and SYSIMETSA (66), BJORK and LODIN (9) or cinefluorography, e g LITWAK et al (67), can give valuable informations about the condition of the mitral valve However, it is difficult to establish whether the calcium deposits are situated in the leaflets or in the annular region, MICHELL (71) The latter location often does not influence the mobility of the leaflets On the other hand, the absence of calcifications does not preclude sclerosis of the leaflets Thus LITWAK et al (67) in a material of 42 patients found 7 with non calcific fibrous valves, in none could satisfactory restoration of function be achieved by closed commissurotomy

EDLER (27) observed a low maximal amplitude of the UCG tracing, 15 mm or less, in mitral stenosis with calcifications of the leaflets As mentioned before, EFFERT (33) found a low amplitude, less than 15 mm, in some patients and considered this to be due to organic changes in the left atrial wall In a recent report JOYNER et al (59) compared the character and substance of the mitral leaflet determined at operation or by necropsy with the ultrasound pattern in 112 patients They found an increase in the width of the echo and a decrease in the antero posterior excursion in patients with thick valves due to calcifications or fibrous tissue SEGAL et al (85) also found a reduced amplitude in patients with fixed and immobile leaflets no values were reported However the relation between the amplitude of the UCG-tracing and the mobility and calcification of the anterior mitral leaflet has not before been statistically evaluated

The mean value of the maximal amplitude in the present series was 20 mm, which is within the lower limit of the normal range found by EFFERT (33) and EDLER (26) In 12 patients the amplitude was definitely reduced, 15 mm or less The mean value of amplitude is higher than that found by KJELLBERG et al (62) in their angiocardiographic studies of the excursions of the anterior leaflet The highest value, 29 mm, found by these authors closely agrees with the highest value in the present series However, the lowest value of maximal amplitude found with the ultrasound technique, 10 mm, exceeds the lowest amplitude, 4 mm, observed by KJELLBERG et al

BOIJSEN and the present author (11) have studied the mobility of the anterior leaflet by angiocardiography and by UCG and the preliminary results show good agreement between the two methods, fig 33 and 34

If the patients of the present study were divided into age groups, it was found that the mean value of the maximal amplitude decreased with increasing age MORROW et al (72) found a clear correlation between age and valve type, the incidence of partially or totally immobile valves was far higher in patients over the age of 35 years

In the present series a significant relation between maximal amplitude and mobility of the anterior leaflet was shown by analysis of variance The amplitude was 15 mm or less in all but one of the five patients with an immobile leaflet on the other hand it was 20 mm or more in 27 of the 32 patients with good mobility of the leaflet One of the latter patients had an amplitude

THE RELATION OF CALCULATED MITRAL VALVE AREA TO UCG-FINDINGS AND TO VALVE AREA ESTIMATED AT OPERATION

The hydraulic formula for calculation of the mitral valve area according to CORLIN and GORLIN (44) was used in the present series to relate the ultrasound echo method to another method using numerical values to evaluate the degree of mitral stenosis

The relation between calculated valve area and UCG findings has not been reported before the author s first communication about the results of the present study (46 47)

As a new method for estimating the mitral valve area at operation was used in the present investigation it also seemed to be of interest to study the *correlation between the values obtained* by this method and those calculated by the CORLIN formula

The mitral valve area was calculated in 44 patients 24 with sinus rhythm and 20 with atrial fibrillation

CALCULATIONS OF VALVE AREAS ON THE BASIS OF REST AND EXERCISE DATA

Areas were calculated from both rest and exercise data in 35 patients, of those 20 had sinus rhythm and 15 atrial fibrillation The mean values were the same 1 73 cm² during rest and exercise in the patients with sinus rhythm the range of the difference was 0 1—1 9 cm² In the patients with atrial fibrillation the mean value at rest was 0 95 cm² and during exercise 1 02 the range of the differences was 0—0 4 cm

THE RELATION BETWEEN DESCENT RATE AND CALCULATED MITRAL VALVE AREA

In the 24 patients with *sinus rhythm* the mean value of descent rate was 17 3 mm/s, the mean valve area was 1 67 cm² The correlation between descent rate and valve area was statistically significant, table 19, fig 35

Three patients deviated most from the regression line in fig 35, namely Nos 96, 143 and 152 The first patient had the highest rate of descent in the present series 27 mm/s and a very large calculated area which was due to a large area calculated on the hemodynamic data at rest 4 3 cm the valve area estimated by the surgeon was 2 1 cm² Case No 143 had a descent rate of 26 mm/s and an area of 1 5 cm², at the operation it was 1 9 cm²

Case No 152 was the only patient with an area exceeding 1 5 cm² at a descent rate of 15 mm/s or less, at the same time he was the only one with a low maximal amplitude 15 mm At the operation the area was estimated at 1 9 cm² the anterior leaflet showed a moderate mobility but the calcifications were of the most advanced type

The correlation between descent rate and valve area was highly significant ($r = 0.67$) if calculated for the 23 patients with a maximal amplitude exceeding 15 mm

In the 20 patients with *atrial fibrillation* the mean value of descent rate was 14 8 mm/s and the mean valve area

lation was not significant for the corresponding patients with atrial fibrillation

3 A coexistent mitral regurgitation did not adversely affect the correlation between descent rate and valve area

4 The maximal amplitude was significantly related to mobility of the anterior leaflet and to calcifications of the mitral valve Patients with a maximal amplitude of 15 mm or less often had immobile and calcified leaflets The amplitude was significantly lower in patients with a regurgitant jet palpable 2 fingers or more from the mitral orifice

5 The origin and significance of the UCG-tracing in relation to the movements of the anterior leaflet in the normal mitral valve and in different types of mitral stenosis is discussed

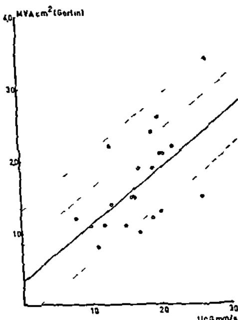

Fig 35 *The relation of the diastolic descent rate to the calculated mitral valve area in patients with sinus rhythm Regression line ± Sy x and 2 Sy x*

15 mm it was still not significant ($r = 0\ 25$)

If the calculated valve area was divided by the body surface area and expressed as a "*mitral valve area index* as discussed in chapter VI the coefficient of correlation for 24 patients with sinus rhythm was 0 70 ($p < 0\ 001$) and 0 26 ($p > 0\ 1$) in 20 patients with atrial fibrillation

The correlation between the descent rate and the *mitral valve area estimated at operation* in this selected series of patients was highly significant ($r = 0\ 66$) in those with sinus rhythm but not significant ($r = 0\ 16$) in the patients with atrial fibrillation

THE RELATION BETWEEN CALCULATED AND SURGICALLY ESTIMATED VALVE AREAS

The correlation between the mitral valve area calculated by the GORLIN formula and that estimated by the surgeon was statistically significant in the patients with *sinus rhythm* table 20,

1 04 cm² table 19 The difference between the patients with sinus rhythm and those with atrial fibrillation was not significant with regard to descent rate but the calculated area was highly significantly smaller in the latter patients

The correlation between descent rate and valve area was not statistically significant in these patients table 19, fig 36 Six patients with descent rates between 10 and 14 mm/s had valve areas which were 1 cm² or smaller but areas of the same size were found in five patients with descent rates between 16 and 20 mm s

Four patients had a low maximal amplitude 12—15 mm When the correlation was calculated only for the patients with an amplitude exceeding

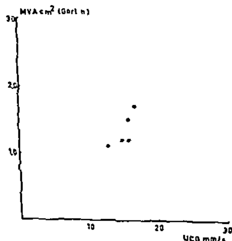

Fig 36 *The relation of the diastolic descent rate to the calculated mitral valve area in patients with atrial fibrillation*

Table 19 *Diastolic descent rate (mm/s) (x) related to calculated mitral valve area (cm²) (y) Correlation and regression*

	n	$\bar{x}$	$\bar{y}$	r	Pr	Regr equation	$Sy\ x$
Sinus rhythm	24	17 3	1 67	0 62	<0 01	y -0 078x+0 33	±0 50
Sinus rhythm Max amp >15 mm	23	17 5	1 65	0 67	<0 001	y=0 084x+0 18	±0 47
Atrial fibrillation	20	14 8	1 04	0 23	>0 1	y=0 022x+0 72	±0 32
Atrial fibrillation Max amp >15 mm	16	15 6	1 04	0 2[illegible]	>0 1	y=0 026x+0 64	±0 35

Table 20 *Mitral valve area (cm²) estimated at operation (x) related to calculated mitral valve area (cm²) (y) Correlation and regression*

	n	$\bar{x}$	$\bar{y}$	r	Pr	Regr equation	$Sy\ x$
Sinus rhythm	24	1 83	1 67	0 [illegible]2	<0 01	y 0 667x+0 45	±0 54
Sinus rhythm Max amp 15 mm	23	1 82	1 65	0 52	<0 05	y 0 662x+0 44	±0 55
Atrial fibrillation	20	1 67	1 04	0 43	0 1	y -0 298x+0 54	±0 30
Atrial fibrillation Max amp >15 mm	16	1 65	1 04	0 36	>0 1	y=0 294x+0 56	±0 34

DISCUSSION

Gorlin's formula has often been subject to criticism partly because of the theoretical considerations underlying the construction of the formula and partly because the use of pulmonary wedge and assumed left ventricular diastolic pressures instead of the real atrio ventricular gradient For a review of this criticism see WERKO (95) In spite of these objections the formula has been widely used "on the premise that the formula may be useful if its results compare favourably with operative and postmortem findings" FOX et al (43)

Several authors have reported good agreement between the mitral valve area found at operation or autopsy and the area calculated by the original GORLIN formula e g GORLIN and GORLIN (44), ARAUJO and LUKAS (3)

Since the introduction of various techniques for left heart catheterization the formula has been modified by using the left atrial—left ventricular filling pressure gradient and diastolic filling period obtained from the left atrial and left ventricular pulse pressure tracings

With this modified formula good agreement between the calculated mitral valve area and that estimated by the surgeon has been reported e g ABELMANN et al (1) and HAMER et al (49) FOX et al (43) found that both types of hydraulic formulae overestimated the area of the valve in comparison with the surgeon's estimate in their series of five patients with very tight mitral stenosis They also compared the values obtained by the original and modified formulae the latter yielded greater values in every case DICKENS et al (19) also found that the areas calculated by the original formula were in general smaller especially in stenosis of a mild degree Thus the discrepancy was less in 11 preoperative cases with an average area of 1 0 cm² where the mean difference was 0 3 cm² than in 11 postoperative cases with an average area of 2 7 cm² and a mean difference between the formulae of 1 1 cm²

The difference in mitral valve areas obtained by the two formulae can hardly be due to the substitution of the left atrial pressure for the pulmonary wedge pressure, most investigators agree that the mean pressure of the latter tracing adequately reflects the mean left atrial pressure for references see WERKO (96)

To assume a value of 5 mm Hg for the left ventricular diastolic pressure would be a more important source of error Thus HAMER and DOW (49) found that the mean left ventricular diastolic pressure averaged 10 mm Hg in a series of mitral stenosis The individual variation was considerable These authors concluded that the use of an arbitrary value will lead to considerable error in the calculation of the mitral valve area if the gradient is small If the gradient is large this error is not so great, especially since the square root of the gradient is used in the formula

In 35 patients with mitral stenosis studied by DICKENS et al (18) the mean left ventricular filling gradient was 13 mm Hg From their data the difference between the square root of PCV 5' and that of the recorded gradient can be calculated in 19 cases the former was larger mean difference 0 67 range 0—1 4 in 12 cases the latter, mean difference 0 77 range 0 1 -1 3 In the case with the greatest difference between these two modes *of expression of* the gradient the mitral valve area was 1 0 cm² if PCV 5' *was used* and 1 5 cm if it was calculated with the measured left *ventricular filling* pressure gradient

The diastolic filling time in Gorlin's *original* formula is measured from the brachial arterial pressure tracing and this might be another source of error DICKENS et al (19) found that this time was consistently longer than that obtained from the left atrial and left

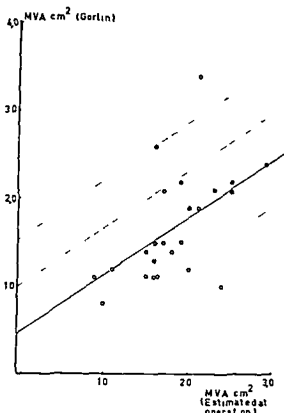

Fig 37 *The relation between the mitral valve areas estimated at operation and calculated by the Gorlin formula in patients with sinus rhythm Regression line* $\pm$ *S y x and 2 S y x*

fig 37 The former averaged 1 67 cm², the latter 1 83 cm², the difference between the mean values was not significant though the surgically estimated area was larger in 18 patients

A close agreement between the areas was found in nine patients in whom no difference was greater than 0 2 cm² In seven patients was the difference 0 5 cm² or more, it was greatest in case No 96 who had a large calculated area as discussed in the preceding section

As mentioned above the correlation between the descent rate of the UCG and the calculated valve area became highly significant when calculated for 23 patients with a maximal amplitude exceeding 15 mm however the correlation between calculated and surgically estimated areas in these patients was only probably significant, table 20

In the patients with *atrial fibrillation* the correlation between the calculated and surgically estimated valve areas was not statistically significant, table 20, fig 38 The former area averaged 1 67 cm² and the latter 1 04 cm², the difference between the mean values being highly significant

As shown by fig 38 the area calculated by the GORLIN formula was smaller than that found at operation in all but one of the patients The areas agreed within 0 2 cm² in only four patients, in eleven the surgically estimated area exceeded the calculated one by more than 0 5 cm²

In these patients also, the correlation was calculated for those with a maximal amplitude exceeding 15 mm The four patients who were thereby excluded had decreased mobility of the anterior leaflet and advanced calcifications, however, the correlation became no stronger $r = 0\ 36$, $p > 0\ 1$

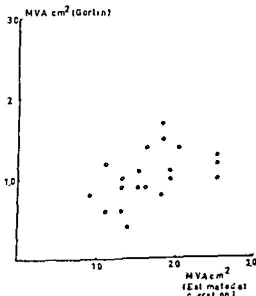

Fig 38 *The relation between the mitral valve areas estimated at operation and calculated by the Gorlin formula in patients with atrial fibrillation*

DISCUSSION

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The diastolic filling time in Gorlin s original formula is measured from the brachial arterial pressure tracing and this might be another source of error DICKENS et al (19) found that this time was consistently longer than that obtained from the left atrial and left

ventricular pressure tracings The difference was greater in stenosis of a mild degree than in more tight stenosis which would be one of the reasons why the original formula yielded smaller areas especially in the former type of stenosis

In the present series the original formula was used since only right heart catheterization data were available Left heart catheterization was not performed as a routine, partly because of the increased risks inherent in this procedure, partly because of the same conditions were desired in the preoperative as in the postoperative hemodynamic eval uation which was later performed in these patients

Valve areas were calculated both in the patients who had none and in those with a minimal regurgitation at operation since it was found by e g ARAUJO and LUKAS (3) and HAMER and DOW (49) that the calculated areas closely agreed with those estimated at operation even in patients with a small degree of mitral insufficiency

The differences between the mitral valve areas calculated from rest and exercise data in the present series were greater than those reported by GORLIN and GORLIN (44) and ARAUJO and LUKAS (3) This would be explained by the composition of the materials, more patients with stenosis of milder degree being included in the present series The work load during exercise was also higher in the present study

The calculated mitral valve area showed a significant correlation to the surgeon s estimate in patients with sinus rhythm, but the former tended to be smaller than the latter Thus 14 patients had a calculated area of 1 5 cm^2 or less In 9 of these the estimated area exceeded this value but in only one ca e was it larger than 2 0 cm^2 A close agreement between the two areas was not found only in the patients with an advanced stenosis The difference between them was not greater than 0 2 cm^2 in nine patients The surgically estimated areas in these patients were evenly distributed between 1 0 and 2 3 cm^2

Case No 96, with an area of 1 3 cm^2 at rest, is an illustration of the statement made by GORLIN and GORLIN (44) that the calculation of valve area is the more inaccurate the lower the pulmonary arterial wedge pressure is They thought it advisable under such circumstances to calculate the valve area on the basis of hemodynamics during exercise In this case the area calculated on exercise data, 2 4 cm^2, also agreed better with the surgical area, which was 2 1 cm^2

The diastolic descent rate of the UCG tracing was significantly correlated to the calculated valve area just as it was to the surgically estimated one The figures of diastolic descent rate would be transferred into valve area by the following expression

$$\frac{\textit{Descent rate mm/s}}{10} = \textit{valve area } cm^2$$

(UCG predicted valve area')

As mentioned, nine patients showed close agreement between calculated and surgically estimated areas with a differ ence not exceeding 0 2 cm^2 Six of the e patients showed a difference of 0—0 2 cm^2 between "UCG predicted valve area and surgical are 1, in the other three patients it was 0 3 cm^2

In order to compare the accuracy of UCG and Gorlin s formula respectively in predicting the mitral valve area at operation the formula $\sqrt{\frac{\Sigma d^2}{2n}}$ was u ed

If "d in the formula was represented by the differences between surgically estimated areas and "UCG-predicted valve area a figure of 0 29 cm^2 was found for the 24 patients with sinus rhythm If calculated for the differences between surgically estimated and Gorlin

areas this figure was 0.39 cm² If these values were expressed in per cent of the mean mitral valve area found at operation a coefficient of variation of 16 % was found for the relation between the former and of 21 % for the relation between the latter areas

Thus the accuracy of the ultrasound echo method was if anything greater than that of the original Gorlin formula in predicting the degree of mitral stenosis found at operation in patients with sinus rhythm

SEGAL et al (85) found descent rates between 10 and 40 mm/s in patients with calculated valve areas between 0 5 and 1 0 cm² 10 of 29 patients with areas of this size had descent rates above 20 mm/s two had rates above 40 mm/s Twenty seven patients with valve areas between 1 0 and 1 5 cm² had descent rates between 30 and 40 mm/s The range of descent rates was thus wider and the values higher than in the present series The e authors used a transducer with a larger diameter (1 9 cm) than in the present study They also seemed to have difficulties in recording the UCG since the transducer was 'sometimes beamed at the mitral leaflet from the apex sometimes the patient was also turned to the right anterior oblique or even more lateral po itions to facilitate the recording

In the patients with atrial fibrillation of the present series the valve area calculated by the Gorlin formula was not significantly correlated to the surgeon s e timate of the area in all but one ca e the latter was underestimated The exclu ion of the patients with a low maximal amplitude in the UCG did not improve the correlation though it would be anticipated that the functional steno is in these ca es would be more advanced than indicated by the valve area found at operation

The di crepancy between calculated and urgically estimated valve areas in the patients with atrial fibrillation could be caused by two main factors 1) the as umed value for left ventricular diastolic pressure was too low and 2) an uneven distribution of the pressure gradient over the left ventricular filling period

The left ventricular diastolic pressure was probably higher than the assumed 5 mm Hg in several cases The patients with atrial fibrillation had significantly larger hearts than those with sinus rhythm which could possibly at least in part be due to myocardial damage al o causing left ventricular dysfunction REALE (77) found that the left ventricular and diastolic pressure was significantly higher before than after restoration of sinus rhythm in 12 patients with mitral valvular disease and atrial fibrillation

Perhaps of greater importance is the observation stressed by GRANATH (45) that a pressure gradient over the mitral ostium was seen only in the first part of diastole in cases with atrial fibrillation who had diastoles of long duration This would mean that the diastolic filling time is overestimated when calculated from the brachial arterial pressure tracing which in turn causes an underestimate of the mitral valve flow per second and thereby of the mitral valve area Six patients of the present series with the greatest discrepancy between calculated and surgically estimated valve areas (0 9—1 3 cm²) also had a low heart rate at rest (26—65 beats/min) four of these had a low rate even during exerci e (53—80 beats/min) In these patients the mentioned factor would be of importance for the poor correlation between the areas

The descent rate of the UCG tracing was not significantly correlated to the urgeon s estimate of the valve area in the e patients with atrial fibrillation The same statistical comparison as in sinus rhythm between Gorlin s formula

and UCG findings in predicting the surgically estimated valve area was not made because of the significant mean difference between calculated and surgically estimated valve areas

However, if an "UCG predicted valve area" was calculated, as for the patients with sinus rhythm, the greatest differences between this area and that estimated by the surgeon were found in three patients case 81 (1 4 cm²) which had a low maximal amplitude and advanced leaflet changes and Nos 92 (0 9 cm²) and 120 (1,2 cm²) in which the discrepancy between UCG findings and valve areas was obscure as discussed in the preceding chapter The corresponding differences between the Gorlin area and surgically estimated valve area were 1 2, 1 3 and 1 5 cm² respectively In 9 of the 17 remaining patients the "UCG-predicted valve area" agreed with the surgically estimated area to within 0 2 cm² The corresponding agreement between calculated and surgically estimated valve areas was found in 4 patients

The four patients with atrial fibrillation and "restenosis" (cases 87, 107, 116 and 127) who had earlier been operated upon for mitral stenosis would be worth a special comment In three of these patients the "UCG predicted valve area" agreed with that found at operation to within 0 2 cm², in the third the difference was 0 3 cm² The corresponding differences between areas calculated by the Gorlin formula and estimated by the surgeon were 0 1—0 3 cm² in two cases and 1 0 cm² in the two other

SUMMARY

The relation between the diastolic descent rate of the UCG tracing and the mitral valve area calculated by the Gorlin formula was studied in 44 patients with mitral stenosis and with no or insignificant mitral regurgitation

The calculated valve area was also correlated to the area estimated by the surgeon

The accuracy of the UCG-finding and the Gorlin area in predicting the mitral valve area found at operation was compared

1 In 24 patients with sinus rhythm the following observations were made

A significant correlation was found between the descent rate and the calculated valve area ($r = 0\ 62$, $p < 0\ 01$) A highly significant correlation ($r = 0\ 67$, $p < 0\ 001$) was found between these variables in 23 patients with a maximal amplitude exceeding 15 mm

The calculated valve area was significantly correlated to the area estimated by the surgeon ($r = 0\ 52$, $p < 0\ 01$)

The descent rate in these patients was also significantly correlated to the surgically estimated area ($r = 0\ 66$ $p < 0\ 001$)

The descent rate in mm/s was divided by 10 and expressed as "UCG predicted valve area" in cm² The coefficient of variation for the differences between this area and that estimated by the surgeon (in per cent of mean surgical area) was 16 %, the corresponding figure for the differences between the latter and the Gorlin area was 21 %

2 In 20 patients with atrial fibrillation no significant correlations were found neither between descent rate and calculated valve area, nor between the latter and the surgically estimated area

The patients showing great difference between "UCG predicted valve area and surgical valve area also showed great difference between the latter and the Gorlin area

In four patients with restenosis of the mitral valve a closer agreement was found between UCG predicted and surgically estimated areas than between the latter and the Gorlin area

3 The possible errors of the original Gorlin formula are discussed

CHAPTER VIII

THE RELATIONSHIP OF SOME CLINICAL AND HEMODYNAMIC DATA TO UCG-FINDINGS AND TO MITRAL VALVE AREAS ESTIMATED AT OPERATION AND BY GORLINS' FORMULA

In mitral stenosis different hemodynamic parameters have been correlated to the valve area calculated by the Gorlin formula by e g LEWIS et al (64) DICKENS et al (18) and HUGENHOLTZ et al (56) This way of correlation has been subject to criticism since pressure and flow is an integral part of the hydraulic formula used to calculate the valve area HARVEY and FERRER (51)

These correlations have generally been made for all patients disregarding the heart rhythm

In the present investigation the degree of mitral stenosis was estimated by three different methods the diastolic descent rate of the UCG the Gorlin formula and finally by the surgeon at the operation It seemed to be of interest to compare these methods with regard to their correlation to hemodynamic data at rest and during exercise and to make this comparison separately for patients with sinus rhythm and with atrial fibrillation

Six variables namely descent rate and maximal amplitude of the UCG tracing mitral valve areas estimated at operation (MVA op) and by the Gorlin formula (MVA Gorlin) both in cm² and cm² m² BSA were correlated to all quantitative variables obtained by clinical examination work test and right heart catheterization and to each other

All correlations were made separately for patients with sinus rhythm and with atrial fibrillation They were performed three times within each rhythm 1) for all patients (descent rate and MVA op) 2) for patients with no or the slightest degree of regurgitation (descent rate, MVA op and MVA Gorlin) and 3) for the same patients and the same variables as in 2) but without those with a maximal amplitude of 15 mm or less to eliminate the influence of advanced leaflet changes upon the descent rate (cf chapter VI)

In addition some other correlations were made namely

Age to heart volume heart rate at work test cardiac output and index mean *pressures and* vascular resistances at rest and during exercise The only significant correlations were found in sinus rhythm to heart volume in ml/m² BSA ($r = 0.49$ $p < 0.01$) and to heart rate during work test ($r = -0.37$ $p < 0.01$)

Cardiac output at rest and during exercise to mean brachial arterial pulmonary arterial and wedge pressures No significant correlations were found

Brachial arterial mean pressure showed no significant correlation to mean pulmonary arterial and wedge pressures at rest and during exercise

Pulmonary arterial mean pressure to pulmonary *arterial* wedge pressure Highly significant correlations were found in patients with *sinus* rhythm at rest ($r = 0.87$) and during exercise ($r = 0$ 8) as well as in those with atrial fibrillation (r = 0.84 and 0.82 respectively)

The *maximal amplitude* of the UCG-tracing showed only 7 statistically significant correlations of about 180 performed in patients with sinus rhythm and only 3 in patients with atrial fibrillation It showed a highly significant correlation to the descent rate in the whole material of patients with sinus

and UCG-findings in predicting the surgically estimated valve area was not made because of the significant mean difference between calculated and surgically estimated valve areas.

However, if an "UCG-predicted valve area" was calculated, as for the patients with sinus rhythm, the greatest differences between this area and that estimated by the surgeon were found in three patients, case 81 (1.4 cm²) which had a low maximal amplitude and advanced leaflet changes and Nos. 92 (0.9 cm²) and 120 (1.2 cm²) in which the discrepancy between UCG-findings and valve areas was obscure as discussed in the preceding chapter. The corresponding differences between the Gorlin area and surgically estimated valve area were 1.2, 1.3 and 1.5 cm² respectively. In 9 of the 17 remaining patients the "UCG-predicted valve area" agreed with the surgically estimated area to within 0.2 cm². The corresponding agreement between calculated and surgically estimated valve areas was found in 4 patients.

The four patients with atrial fibrillation and restenosis (cases 87, 107, 116 and 127) who had earlier been operated upon for mitral stenosis would be worth a special comment. In three of these patients the "UCG-predicted valve area" agreed with that found at operation to within 0.2 cm², in the third the difference was 0.3 cm². The corresponding differences between areas calculated by the Gorlin formula and estimated by the surgeon were 0.1—0.3 cm² in two cases and 1.0 cm² in the two other.

SUMMARY

The relation between the diastolic descent-rate of the UCG-tracing and the mitral valve area calculated by the Gorlin formula was studied in 44 patients with mitral stenosis and with no or insignificant mitral regurgitation.

The calculated valve area was also correlated to the area estimated by the surgeon.

The accuracy of the UCG-finding and the Gorlin area in predicting the mitral valve area found at operation was compared.

1. In 24 patients with sinus rhythm the following observations were made.

A significant correlation was found between the descent-rate and the calculated valve area ($r = 0.62$, $p < 0.01$). A highly significant correlation ($r = 0.67$, $p < 0.001$) was found between these variables in 23 patients with a maximal amplitude exceeding 15 mm.

The calculated valve area was significantly correlated to the area estimated by the surgeon ($r = 0.52$, $p < 0.01$).

The descent-rate in these patients was also significantly correlated to the surgically estimated area ($r = 0.66$, $p < 0.001$).

The descent-rate in mm/s was divided by 10 and expressed as "UCG-predicted valve area" in cm². The coefficient of variation for the differences between this area and that estimated by the surgeon (in per cent of mean surgical area) was 16 %, the corresponding figure for the differences between the latter and the Gorlin area was 21 %.

2. In 20 patients with atrial fibrillation no significant correlations were found neither between descent-rate and calculated valve area, nor between the latter and the surgically estimated area.

The patients showing great difference between "UCG-predicted valve area" and surgical valve area also showed great difference between the latter and the Gorlin area.

In four patients with restenosis of the mitral valve a closer agreement was found between UCG-predicted and surgically estimated areas than between the latter and the Gorlin area.

3. The possible errors of the original Gorlin formula are discussed.

THE RELATIONSHIP OF SOME CLINICAL AND HEMODYNAMIC DATA TO UCG-FINDINGS AND TO MITRAL VALVE AREAS ESTIMATED AT OPERATION AND BY GORLINS' FORMULA

In mitral stenosis different hemodynamic parameters have been correlated to the valve area calculated by the Gorlin formula, by e g LEWIS et al (64) DICKENS et al (18) and HUGENHOLTZ et al (56) This way of correlation has been subject to criticism since pressure and flow is an integral part of the hydraulic formula used to calculate the valve area, HARVEY and FERRER (51)

These correlations have generally been made for all patients disregarding the heart rhythm

In the present investigation the degree of mitral stenosis was estimated by three different methods the diastolic *descent rate of the UCG*, the Gorlin formula and finally by the surgeon at the operation It seemed to be of interest to compare these methods with regard to their correlation to hemodynamic data at rest and during exercise and to make this comparison separately for patients with sinus rhythm and with atrial fibrillation

Six variables namely descent rate and maximal amplitude of the UCG tracing mitral valve areas estimated at operation (MVA op) and by the Gorlin formula (MVA Gorlin) both in cm² and cm²/m² BSA were correlated to all quantitative variables obtained by clinical examination work test and right heart catheterization and to each other

All correlations were made separately for patients with sinus rhythm and with atrial fibrillation They were performed three times within each rhythm 1) for all patients (descent rate and MVA op), 2) for patients with no or the slightest degree of regurgitation (descent rate MVA op and MVA Gorlin) and 3) for the same patients and the same variables as in 2), but without those with a maximal amplitude of 15 mm or less to eliminate the influence of advanced leaflet changes upon the descent rate (cf chapter VI)

In addition some other correlations were made namely

Age to heart volume heart rate at work test cardiac output and index mean pressures and vascular resistances at rest and during exercise The only significant correlations were found in sinus rhythm to heart volume in ml/m² BSA ($r = 0.49$ $p < 0.01$) and to heart rate during work test ($r = -0.47$ $p < 0.01$)

Cardiac output at rest and during exercise to *mean brachial arterial* pulmonary arterial and wedge pressures No significant correlations were found

Brachial arterial mean pressure showed no significant correlation to *mean pulmonary* arterial and wedge pressures at rest and during exercise

Pulmonary arterial mean pressure to pulmonary *arterial wedge pressure* Highly significant correlations were found in patients with *sinus* rhythm at rest ($r = 0.87$) and during exercise (r 0.78) as well as in those with atrial fibrillation ($r = 0.84$ and 0.82 respectively)

The *maximal amplitude* of the UCG tracing showed *only* 7 statistically significant correlations of about 180 performed in patients with sinus rhythm *and only* 3 *in* patients with atrial fibrillation It showed a highly significant correlation to the descent rate in the whole material of patients with sinus

Table 21 *Diastolic descent rate of UCG and surgeon's estimate of mitral valve area (MVA op) related to clinical and hemodynamic data in all patients with sinus rhythm.*

	Descent rate (mm/s)		*MVA op* (cm²)	
	n	*r*	*n*	*r*
Age (years)	39	−0.06	39	0.32*
Duration (years) *from rheum. fever*	25	−0.15	25	0.33
Heart volume (ml/m² BSA)	39	−0.24	39	0.19
Work test (Heart rate beats/min)	39	0.19	39	−0.17
UCG				
Descent rate (mm/s)	—	—	39	0.60***
Maximal amplitude (mm)	39	0.51***	39	0.11
MVA (cm²)				
Surgeon's estimate	39	0.60***	—	—
Gorlin formula	24	0.62**	24	0.52**
Cardiac index (l/min/m²)				
Fick				
Rest	31	0.39*	31	0.45*
Exercise	31	0.23	31	0.25
BSP				
Rest	35	0.47**	35	0.45**
Exercise	32	0.32	32	0.42*
Stroke index (ml/beat/m²)				
Fick				
Rest	31	0.03	31	0.24
Exercise	31	−0.02	31	0.13
BSP				
Rest	35	0.13	35	0.33
Exercise	32	0.09	32	0.29
Oxygen consumption (ml/min STPD)				
Rest	33	−0.25	33	0.04
Exercise	31	−0.35	31	−0.01
A–V oxygen difference (ml/l)				
Rest	33	−0.64***	33	−0.43*
Exercise	32	−0.37*	32	−0.14

	Descent rate (mm/s)		MVA op (cm)	
	n	*r*	*n*	*r*
Pressures (Mean pressures mm Hg)				
Brachial artery				
Rest	35	0.23	35	0.21
Exercise	30	0.04	30	0.10
Pulmonary artery				
Rest	37	−0.42**	37	−0.42
Exercise	34	−0.62***	34	−0.32
Pulm. art. wedge				
Rest	37	−0.51*	37	−0.46**
Exercise	34	−0.50*	34	−0.45*
Right atrium				
Rest	23	0.33	23	−0.01
Exercise	26	−0.27	26	−0.36
Vascular resistance (units)				
Systemic circulation				
Rest	35	−0.13	35	−0.25
Exercise	30	−0.02	30	−0.05
Pulmonary circulation				
Rest	35	−0.21	35	−0.35*
Exercise	32	−0.48*	32	−0.07

Table 22. *Diastolic descent rate of UCG, surgeon's estimate of mitral valve area (MVA op.) and calculated mitral valve area (MVA Gorlin) related to clinical and hemodynamic data in patients with sinus rhythm (mitral regurgitation 0 or (+) and maximal amplitude > 15 mm)*

	Descent rate (mm/s)		MVA op (cm²)		MVA Gorlin (cm²)	
	n	*r*	*n*	*r*	*n*	*r*
Age (years)	26	0.18	26	0.49*	23	−0.12
Duration (years) *from rheum. fever*	13	0.11	13	0.52	13	−0.07
Heart volume (ml/m² BSA)	26	0.11	26	0.23	23	−0.09
Work test (Heart rate beats/min)	26	0.15	26	−0.25	23	0.07
UCG						
Descent rate (mm/s)	—	—	26	0.64	23	0.68
Maximal amplitude (mm)	26	0.31	26	0.05	23	0.32
MVA (cm²)						
Surgeon's estimate	26	0.64***	—	—	23	0.52*
Gorlin formula	23	0.68*	23	0.52	—	—

(Table 22 continued)

	Descent rate (mm/s)		*MVA op* (cm^2)		*MVA Gorlin* (cm^2)	
	n	*r*	*n*	*r*	*n*	*r*
Cardiac index (l/min/m^2)						
Fick						
Rest	21	0.28	21	0.46*	21	0.54*
Exercise	21	−0.06	21	0.05	21	0.13
BSP						
Rest	23	0.49*	23	0.53*	23	0.58**
Exercise	21	0.25	21	0.52*	21	0.32
Stroke index (ml/beat/m^2)						
Fick						
Rest	21	−0.03	21	0.28	21	0.35
Exercise	21	0.07	21	0.24	21	0.24
BSP						
Rest	23	0.27	23	0.50*	23	0.48*
Exercise	21	0.24	21	0.52*	21	0.31
Oxygen consumption (ml/min STPD)						
Rest	21	−0.05	21	0.10	21	0.11
Exercise	21	−0.21	21	0.14	21	0.04
A—V oxygen difference (ml/l)						
Rest	23	−0.51*	23	−0.43*	23	−0.49*
Exercise	21	−0.15	21	0.03	21	−0.02
Pressures (Mean pressures mm Hg)						
Brachial artery						
Rest	23	0.46*	23	0.30	23	−0.04
Exercise	19	0.39	19	0.19	19	−0.13
Pulmonary artery						
Rest	25	−0.59**	25	−0.49*	23	−0.61**
Exercise	23	−0.62**	23	−0.41	21	−0.65**
Pulm art wedge						
Rest	25	−0.62**	25	−0.51**	23	−0.67***
Exercise	23	−0.66***	23	−0.54**	21	−0.75***
Right atrium						
Rest	14	0.25	14	−0.08	14	−0.18
Exercise	17	−0.40	17	−0.48*	15	−0.42
Vascular resistance ('units')						
Systemic circulation						
Rest	23	−0.09	23	−0.24	23	−0.51*
Exercise	19	0.41	19	−0.01	19	−0.13
Pulmonary circulation						
Rest	23	−0.39	23	−0.44*	23	−0.48*
Exercise	21	−0.35	21	−0.22	21	−0.34

Table 23 *D as ol c descent ra e of UCG (mm/s) su geon s es mate of m tral val e area (MVA op cm²) and calculated m tral valve area (MVA Gorl n cm²) related to son e hemodynam c d ta in pat ents w th s nus rhythm (m tral regurgitat on 0 or (+) and maxim al ampl tude >15 mm)*

Correlat on and reg essio

Card c in lex (l/m n/m²) at rest (y)

(x)	n	$\bar{x}$	$\bar{y}$	r	P r	Regr equat o	Sy x
De e t rate	23	17	3.12	0 4)	(0.5	y 0 0)2x + 1 81	± 0.81
MVA	23	1.8?	3.12	0.53	0 0	y (99(x + 1 (0	± 0.8.
MVA G l	23	1.6	3.12	0.58	< 0.01	y 0.86 x + 1)9	± 0.7)

P uln ry rt al m e n press re (m m Hg) t rest (y)

(x)	n	$\bar{x}$	$\bar{y}$	r	P r	Regr e t o	Sy x
Desce t rate	2	17.5	26.7	−0.59	<0.01	y — 1.297x + 49.4	± 9.0
MVA op	25	1.79	26.7	−0.49	<0.05	y −10.67 x + 45.8	± 9.7
MVA G rl	23	1.65	26.7	−0.61	<0.01	y −11.12 x + 4 0	± 9.2

P ulm onary arterial m ean pressure (m m Hg) during exercise (y)

(x)	n	$\bar{x}$	$\bar{y}$	r	P r	Regr equation	Sy x
Descent rate	23	18.1	48.0	−0.62	<0.01	y = — 1.915x + 82.6	±11.1
MVA op	23	1.86	48.0	−0.41	<0.10	y = −12.92 x + 72.0	±13.3
MVA Gorl n	21	1.71	47.8	−0.65	<0.01	y −15.69 x + 74.7	±11.4

P ul onary a ter al wedge pressure (mm Hg) at rest (y)

(x)	n	$\bar{x}$	$\bar{y}$	r	P r	Regr equat o	Sy x
Descent rate	25	17.5	17.4	−0.62	<0.01	y — 0.953x + 34.1	± 6.2
MVA	25	1.7)	17.4	−0.51	<0.01	y — 7.788x + 31.3	± 6.7
MVA (rl	23	1.65	17.2	−0.67	<0.001	y = — 8.525x + 31.3	± 6.0

P ulm o ary a ter l edge pressure (m Hg) during exercise (y)

(x)	n	$\bar{x}$	$\bar{y}$	r	P r	Regr equat o	Sy x
Desce t rate	23	18.1	35.3	−0.66	<0.001	y — 1.466x + 61.8	± 7.9
MVA op	23	1.86	35.3	−0.54	<0.01	y = −12.23 x + 58.1	± 8.9
MVA Gorl n	21	1.71	34.8	−0.75	<0.001	y −12.28 x + 55.8	± 6.8

(Table 22 continued)

	Descent rate (mm/s)		*MVA op* (cm)		*MVA Gorlin* (cm²)	
	n	*r*	*n*	*r*	*n*	*r*
Cardiac index (l/min/m²)						
Fick						
Rest	21	0.28	21	0.46*	21	0.54*
Exercise	21	−0.06	21	0.05	21	0.13
BSP						
Rest	23	0.49*	23	0.53*	23	0.58**
Exercise	21	0.25	21	0.52*	21	0.32
Stroke index (ml/beat/m²)						
Fick						
Rest	21	−0.03	21	0.28	21	0.35
Exercise	21	0.07	21	0.24	21	0.24
BSP						
Rest	23	0.27	23	0.50*	23	0.48*
Exercise	21	0.24	21	0.52*	21	0.31
Oxygen consumption (ml/min STPD)						
Rest	21	−0.05	21	0.10	21	0.11
Exercise	21	−0.21	21	0.14	21	0.04
A—V oxygen difference (ml/l)						
Rest	23	−0.51*	23	−0.43*	23	−0.49*
Exercise	21	−0.15	21	0.03	21	−0.02
Pressures (Mean pressures mm Hg)						
Brachial artery						
Rest	23	0.46*	23	0.30	23	−0.04
Exercise	19	0.39	19	0.19	19	−0.13
Pulmonary artery						
Rest	25	−0.59**	25	−0.49*	23	−0.61**
Exercise	23	−0.62**	23	−0.41	21	−0.65**
Pulm art wedge						
Rest	25	−0.62**	25	−0.51**	23	−0.67***
Exercise	23	−0.66***	23	−0.54**	21	−0.75***
Right atrium						
Rest	14	0.25	14	−0.08	14	−0.18
Exercise	17	−0.40	17	−0.48*	15	−0.42
Vascular resistance (units)						
Systemic circulation						
Rest	23	−0.09	23	−0.24	23	−0.51*
Exercise	19	0.41	19	−0.01	19	−0.13
Pulmonary circulation						
Rest	23	−0.39	23	−0.44*	23	−0.48*
Exercise	21	−0.35	21	−0.22	21	−0.34

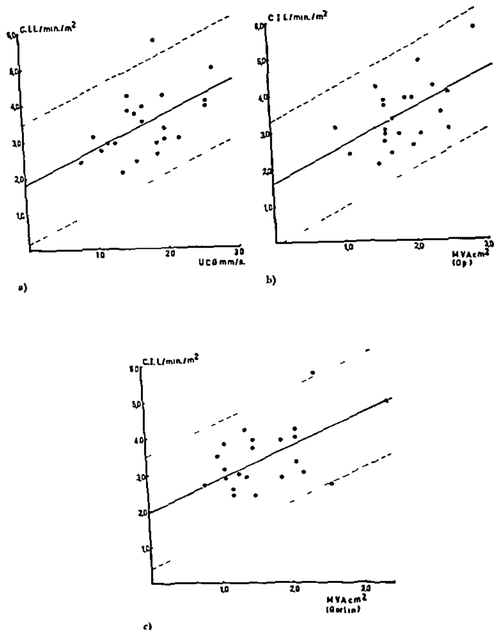


Fig. 39 The relation of the cardiac index (BSI) at rest to a) diastolic descent rate b) MVA op and c) MVA Gorlin in patients with sinus rhythm mitral regurgitation 0 or (+) and maximal amplitude > 15 mm Regression line ± 2 S y x

rhythm (table 21), if the patients with amplitude $\leq$ 15 mm were excluded the correlation was not significant

The *mitral valve area related to BSA* showed only small and occasional differences in the level of statistical significance compared to the simple area So only the correlations of the latter will be shown when the results are presented

PATIENTS WITH SINUS RHYTHM

Table 21 shows the coefficients of correlation for the relations of the descent rate and MVA op to clinical and hemodynamic data and to each other in all patients with sinus rhythm, table 22 those of the three variables in patients with no or the slightest degree of mitral regurgitation and with a maximal amplitude exceeding 15 mm ("selected material")

CLINICAL DATA

The only relation of any statistical significance was the probably significant positive correlation between MVA op and age, which was due to the fact that five of six patients with MVA 2 2 cm^2 or larger were about 50 years of age or older

HEMODYNAMIC DATA

Blood flow parameters

No significant correlation was found between the *oxygen consumption* at rest and during exercise and the three variables

Cardiac output and index All patients Cardiac index (Fick) at rest was probably significantly correlated to descent rate and to MVA op, while the correlation between cardiac index (BSP) and these two variables was statistically significant

Selected material The relation of the cardiac index (BSP) at rest to the three variables in the patients of table 22 is shown by fig 39, the regression equations are shown in table 23 In these patients the cardiac index was significantly correlated to the Gorlin area while the correlation to the descent rate and MVA op was probably significant

Fig 39 shows that cardiac indices below 3 l/min/m^2 were evenly distributed between descent rates of 10—20 mm/s and surgically estimated areas of 1 0—2 0 cm^2 while most of them were found in calculated areas less than 1 5 cm^2 The lowest index, 2 1 l/min/m^2, was found in case 79 which had both a low descent rate and small valve areas

Cardiac index (BSP) during exercise showed a probably significant correlation to MVA op, otherwise no significant correlations were found between cardiac output or index during exercise and the three variables

Stroke volume and index Stroke index (BSP) at rest was probably significantly correlated to MVA op and Gorlin during exercise this stroke index showed the same relation only to MVA op (table 22)

Arterio venous oxygen difference In all patients with sinus rhythm (table 21) a highly significant inverse relationship was found to descent rate and a probably significant one to MVA op (at rest) Fig 40 shows that all but one patient with an arterio venous oxygen difference below 40 ml/l had descent rates of 20 mm/s or higher The highest value, 63 ml/l, was found in case 75 with the lowest descent rate 7 mm/s, in the UCG-tracing, which also showed a low maximal amplitude MVA op in this case was 2 1 cm^2 but the leaflets were calcified with restricted mobility

In the selected material the value at rest showed a probably significant correlation to the three variables (table 22)

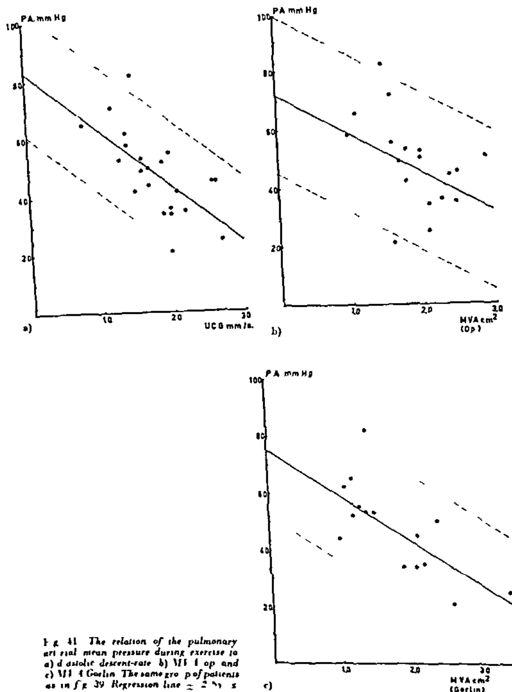


Fig. 41 The relation of the pulmonary arterial mean pressure during exercise to a) diastolic descent-rate b) MVA op and c) MVA Gorlin The same group of patients as in fig 39 Regression line ± 2 SD's

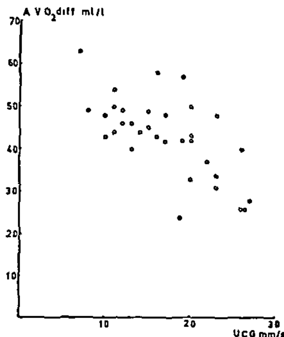


Fig 40 *The relation of the arterio-venous oxygen difference at rest to the diastolic descent rate in patients with sinus rhythm*

Mean pressures in the systemic and pulmonary circulation

Brachial arterial pressure No significant correlations were found

Pulmonary arterial pressure In all the patients (table 21) a significant inverse relationship was found to descent rate both at rest and during exercise while the correlation to MVA op was only probably significant at rest and not significant during exercise

In the selected material (table 22) the pressure at rest and during exercise was significantly correlated to both descent-rate and MVA Gorlin while the relationship to MVA op was probably significant only at rest

Fig 41 shows the relation of the pulmonary arterial mean pressure during exercise to the three variables (regression equations in table 23) The pressure of 82 mm Hg in case 108 was higher than would be expected in relation to all the three variables, this patient also had the highest value of calculated pulmonary vascular resistance of these patients 3 8 units At the other extreme was case 135 with a normal mean pressure during exercise, 21 mm Hg, though a stenosis of a significant degree was found at operation, 1 6 cm² This pressure was also low in relation to the descent rate, it was best related to the Gorlin area of 2 6 cm² —Even if the correlation to MVA op was not statistically significant, fig 41 shows that mean pressures exceeding 60 mm Hg were found only with an area of 1 6 cm² or less, the corresponding descent rates and Gorlin areas were 15 mm/s and 1 5 cm² respectively

Pulmonary arterial wedge pressure In all the patients (table 21) significant negative correlations were found to *descent-rate* and MVA op at rest and during exercise

In the selected material (table 22) the wedge pressure at rest and during exercise showed statistically significant or highly significant inverse relationships to all the three variables, the regression equations are shown in table 23 At rest six patients had wedge pressures within the normal range (12 mm Hg or less) of these patients five had descent rates of 20 mm/s or higher four had a MVA op larger than 2 0 cm² and five a Gorlin area of this size Six patients had pressures above 20 mm Hg, all had descent rates of $\leq$ 15 mm/s, MVA op $\leq$ 1 6 cm² and MVA Gorlin $<$ 1 5 cm²

Fig 42 illustrates the relationship of the wedge pressure during exercise to the descent rate and mitral valve areas Most pressures above 40 mm Hg were found at descent rates of $\leq$ 15 mm/s, MVA op of $\leq$ 1 6 cm² and MVA Gorlin $\leq$ 1 5 cm² Those below 30 mm Hg generally corresponded to descent rates of 20 mm/s, to MVA op and Gorlin $>$ 2 0 cm²

Even the wedge pressure in case 135 was low in relation to the descent rate and MVA op. Case 113 had a wedge pressure of 38 mm Hg at a descent rate of 26 mm/s and a MVA op. of 2.5 cm². In this patient an extreme difference was observed between the wedge pressures recorded after 5 and 10 minutes exercise; it decreased from 38 to 23 mm Hg. The latter pressure was more closely related to the UCG finding and to MVA op. but the former was used for the correlation because pressures usually were recorded after five minutes exercise.

Right atrial pressure. The only correlation of any statistical significance was the inverse relationship between this pressure during exercise and MVA op. (table 22).

Vascular resistance

Systemic vascular resistance. A probably significant negative correlation was found between this resistance at rest and the Gorlin area.

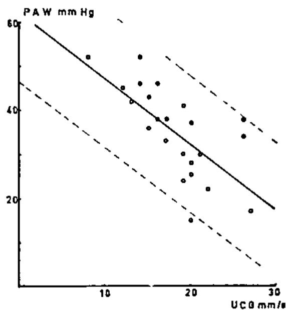
Pulmonary vascular resistance. An inverse relationship was found to descent rate and valve areas in the patients of table 21 the correlation between resistance during exercise and descent rate was statistically significant. This correlation was especially caused by case 75 with a resistance of 6.9 units at a descent rate of 7 mm/s. As discussed above this patient had a MVA op. of 2.1 cm² which contributed to the not significant relation to this variable. The next highest values of resistance, 3.8 and 3.2 units, corresponded to descent rates of 15 and 12 mm/s respectively. Values below 1.0 unit were only found at descent rates of ≥ 15 mm/s and at MVA op. of ≥ 1.6 cm².

PATIENTS WITH ATRIAL FIBRILLATION

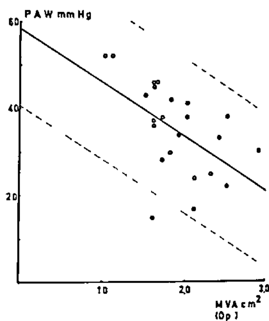
Table 24 shows the coefficients of correlation in all patients with atrial fibrillation, those in patients with no or the slightest degree of mitral regurgitation and a maximal amplitude exceeding 15 mm ("selected material") are shown in table 25.

Table 24. *Diastolic descent rate of UCG and surgeon's estimate of mitral valve area (MVA op.) related to clinical and hemodynamic data in all patients with atrial fibrillation*

	Descent rate (mm/s)		MVA op. (cm²)	
	n	r	n	r
Age (years)	32	−0.06	32	−0.06
Duration (years) from rheum. fever	19	−0.07	19	0.15
Heart volume (ml/m² BSA)	32	−0.43y	32	−0.05
Work test (Heart rate, beat/min)	31	−0.03	31	−0.25
UCG				
Descent rate (mm/s)	—	—	32	0.27
Maximal amplitude (mm)	32	0.32	32	−0.03
MVA (cm²)				
Surgeon's estimate	32	0.2	—	—
Gorlin formula	20	0.23	20	0.43



a)



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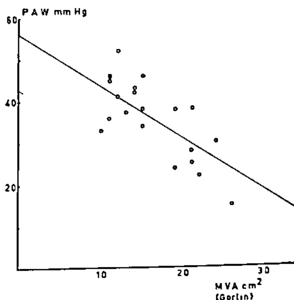


c)

Fig. 42. The relation of the pulmonary arterial wedge pressure during exercise to a) diastolic descent rate b) MVA op. and c) MVA Gorlin. The same group of patients as in fig. 39. Regression line $\pm 2 S_{y \cdot x}$

Table 25 *Diastolic descent rate of UCG surgeon's estimate of mitral valve area (MVA op) and calculated mitral valve area (MVA Gorlin) related to clinical and hemodynamic data in patients with atrial fibrillation (mitral regurgitation 0 or (+) and maximal amplitude > 15 mm)*

	Descent rate (mm/s)		*MVA op* (cm²)		*MVA Gorlin* (cm²)	
	n	*r*	*n*	*r*	*n*	*r*
Age (years)	20	—0.13	20	0.06	16	—0.28
Duration (years) *from rheum fever*	10	0.24	10	0.35	9	0.00
Heart volume (ml/m² BSA)	20	—0.44	20	0.12	16	—0.19
Work test (Heart rate beats/min)	19	0.06	19	—0.18	15	0.35
UCG						
Descent rate (mm/s)	—	—	20	0.28	16	0.25
Maximal amplitude (mm)	20	0.02	20	—0.05	16	0.16
MVA (cm²)						
Surgeon's estimate	20	0.28	—	—	16	0.36
Gorlin formula	16	0.25	16	0.36	—	—
Cardiac index (l/min m²)						
Fick						
Rest	13	—0.04	13	0.19	13	0.40
Exercise	14	0.32	14	—0.11	14	0.56*
BSP						
Rest	14	0.11	14	0.42	13	0.36
Exercise	13	0.03	13	0.03	12	0.15
Stroke index (ml beat m²)						
Fick						
Rest	13	—0.11	13	0.09	13	0.17
Exercise	14	0.43	14	0.30	14	0.40
BSP						
Rest	14	0.01	14	0.38	13	0.28
Exercise	13	0.10	13	0.58*	12	0.33
Oxygen consumption (ml min STPD)						
Rest	14	—0.08	14	0.25	14	0.02
Exercise	15	0.17	15	—0.22	15	0.31
A—V oxygen difference (ml l)						
Rest	16	—0.10	16	—0.26	15	—0.49
Exercise	14	—0.3*	14	—0.36	14	—0.53

(Table 24 continued)

	Descent rate (mm/s)		MVA op (cm^2)	
	n	*r*	*n*	*r*
Cardiac index ($l/min/m^2$)				
Fick				
Rest	24	0.04	24	0.10
Exercise	23	0.38	23	— 0.04
BSP				
Rest	25	0.23	25	0.25
Exercise	22	0.16	22	— 0.08
Stroke index ($ml/beat/m^2$)				
Fick				
Rest	24	— 0.17	24	0.24
Exercise	23	0.13	23	0.34
BSP				
Rest	25	0.03	25	0.40
Exercise	22	— 0.07	22	0.32
Oxygen consumption (ml/min STPD)				
Rest	25	— 0.26	25	— 0.10
Exercise	24	— 0.01	24	— 0.27
A—V oxygen difference (ml/l)				
Rest	28	— 0.25	28	— 0.33
Exercise	23	— 0.51*	23	— 0.45*
Pressures (Mean pressures mm Hg)				
Brachial artery				
Rest	28	— 0.13	28	0.00
Exercise	23	— 0.10	23	0.27
Pulmonary artery				
Rest	30	— 0.44*	30	— 0.43*
Exercise	25	— 0.44*	25	— 0.53**
Pulm art wedge				
Rest	29	— 0.23	29	— 0.25
Exercise	23	— 0.25	23	— 0.37
Right atrium				
Rest	17	— 0.17	17	— 0.25
Exercise	22	— 0.25	22	0.10
Vascular resistance (units)				
Systemic circulation				
Rest	27	— 0.06	27	— 0.15
Exercise	23	— 0.39	23	0.10
Pulmonary circulation				
Rest	27	— 0.52**	27	— 0.53**
Exercise	23	— 0.52*	23	— 0.57**

Table 25 *Diastolic descent rate of UCG surgeon's estimate of mitral valve area (MVA op) and calculated mitral valve area (MVA Gorlin) related to clinical and hemodynamic data in patients with atrial fibrillation (mitral regurgitation 0 or (+) and maximal amplitude > 15 mm)*

	Descent rate (mm/s)		*MVA op* (cm²)		*MVA Gorlin* (cm²)	
	n	*r*	*n*	*r*	*n*	*r*
Age (years)	20	−0.13	20	0.06	16	−0.28
Duration (years) *from rheum fever*	10	0.24	10	0.35	9	0.00
Heart volume (ml/m² BSA)	20	−0.44	20	0.12	16	−0.19
Work test (Heart rate beat/min)	19	0.06	19	−0.18	15	0.35
UCG						
Descent rate (mm/s)	—	—	20	0.28	16	0.25
Maximal amplitude (mm)	20	0.02	20	−0.05	16	0.16
MVA (cm²)						
Surgeon's estimate	20	0.28	—	—	16	0.36
Gorlin formula	16	0.25	16	0.36	—	—
Cardiac index (l/min m²)						
Fick						
Rest	13	−0.04	13	0.19	13	0.40
Exercise	14	0.32	14	−0.11	14	0.56*
BSP						
Rest	14	0.11	14	0.42	13	0.36
Exercise	13	0.03	13	0.03	12	0.15
Stroke index (ml/beat/m²)						
Fick						
Rest	13	−0.11	13	0.09	13	0.17
Exercise	14	0.43	14	0.30	14	0.40
BSP						
Rest	14	0.01	14	0.38	13	0.28
Exercise	13	0.10	13	0.58*	12	0.33
Oxygen consumption (ml/min STPD)						
Rest	14	−0.08	14	0.25	14	0.02
Exercise	15	0.17	15	−0.22	15	0.31
A—V oxygen difference (ml/l)						
Rest	16	−0.10	16	−0.26	15	−0.49
Exercise	14	−0.37	14	−0.36	14	−0.53

(Table 24 continued)

	Descent rate (mm/s)		MVA op (cm²)	
	n	*r*	*n*	*r*
Cardiac index (l/min/m²)				
Fick				
Rest	24	0 04	24	0 10
Exercise	23	0 38	23	— 0 04
BSP				
Rest	25	0 23	25	0 25
Exercise	22	0 16	22	— 0 08
Stroke index (ml/beat/m²)				
Fick				
Rest	24	— 0 17	24	0 24
Exercise	23	0 13	23	0 34
BSP				
Rest	25	0 03	25	0 40
Exercise	22	— 0 07	22	0 32
Oxygen consumption (ml/min STPD)				
Rest	25	— 0 26	25	— 0 10
Exercise	24	— 0 01	24	— 0 27
A—V oxygen difference (ml/l)				
Rest	28	— 0 25	28	— 0 33
Exercise	23	— 0 51*	23	— 0 45*
Pressures (Mean pre ures mm Hg)				
Brachial artery				
Rest	28	— 0 13	28	0 00
Exercise	23	— 0 10	23	0 27
Pulmonary artery				
Rest	30	— 0 44*	30	— 0 43*
Exercise	25	— 0 44*	25	— 0 53**
Pulm art wedge				
Rest	29	— 0 23	29	— 0 25
Exerci e	23	— 0 25	23	— 0 37
Right atrium				
Rest	17	— 0 17	17	— 0 25
Exercise	22	— 0 25	22	0 10
Vascular resistance (units)				
Systemic circulation				
Rest	27	— 0 06	27	— 0 15
Exercise	23	— 0 39	23	0 10
Pulmonary circulation				
Rest	27	— 0 52**	27	— 0 53*
Exerci e	23	— 0 52*	23	— 0 57**

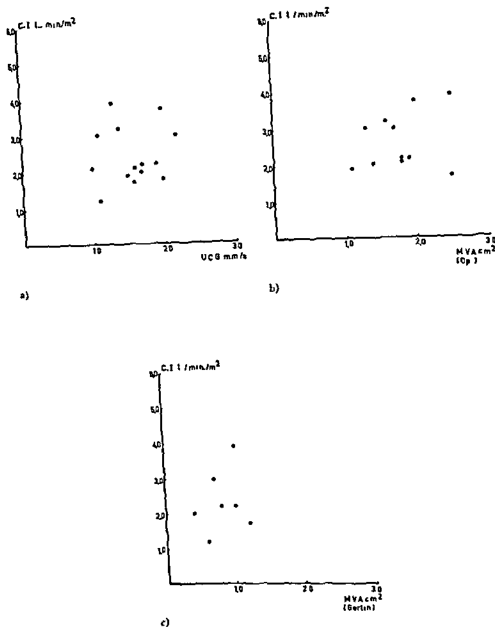


Fig 43 The relation of the cardiac index (BSP) at rest to a) diastolic descent rate b) MVA op and c) MVA Gorlin in patients with atrial fibrillation mitral regurgitation 0 or (+) and maximal amplitude $>$ 15 mm

(Table 25 continued)

	Descent rate (mm/s)		MVA op (cm²)		MVA Gorlin (cm²)	
	n	*r*	*n*	*r*	*n*	*r*
Pressures (Mean pressures, mm Hg)						
Brachial artery						
Rest	16	−0.15	16	0.09	16	−0.21
Exercise	15	−0.31	15	0.19	15	−0.38
Pulmonary artery						
Rest	18	−0.36	18	−0.15	16	−0.18
Exercise	16	−0.55*	16	−0.46	15	−0.37
Pulm art wedge						
Rest	18	−0.25	18	−0.16	16	−0.38
Exercise	14	−0.40	14	−0.46	14	−0.36
Right atrium						
Rest	10	−0.38	10	−0.05	9	−0.80**
Exercise	14	−0.34	14	0.21	13	−0.00
Vascular resistance (units)						
Systemic circulation						
Rest	15	−0.10	15	−0.26	15	−0.47
Exercise	15	−0.53*	15	0.05	15	−0.61*
Pulmonary circulation						
Rest	16	−0.60*	16	−0.37	15	−0.27
Exercise	14	−0.67**	14	−0.40	14	−0.54*

CLINICAL DATA

The heart volume showed a probably significant negative correlation to the descent rate, otherwise no correlations *of any statistical significance were found*

HEMODYNAMIC DATA

Blood flow parameters

The *oxygen consumption* at rest and during exercise was not significantly correlated to any *of the three variables*

Cardiac output and index Cardiac index (Fick) *during exercise showed* a probably significant correlation to the Gorlin area, all other correlations were of no statistical significance

Fig 43 illustrates the relation of cardiac index (BSP) at rest to the three variables in the patients corresponding to *those with sinus rhythm in fig* 39

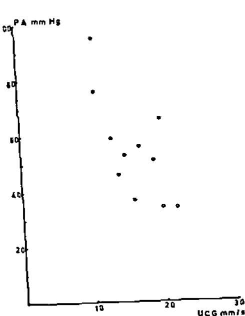
The index showed the best correlation to MVA op, however, the next lowest index was found in case 92 with an area of 2.5 cm²

Stroke volume and index The *stroke index (BSP) during exercise showed a* probably significant correlation to MVA op in the patients of table 25

Arterio venous oxygen difference The values obtained during exercise showed an inverse relationship to descent rate and to MVA op which was probably significant (table 24) Fig 44 illustrates *the relation to the descent rate*

Mean pressures in the systemic and pulmonary circulation

Brachial arterial pressure No significant correlation was found between this pressure at rest and during exercise and any of the three variables



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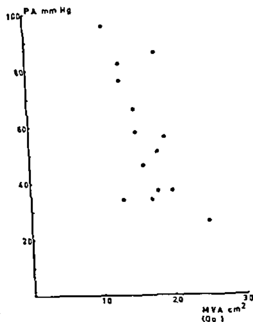

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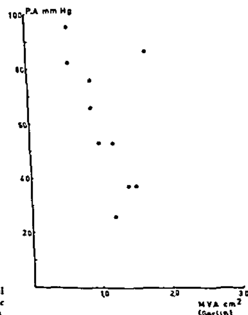

c

Fig 45 The relation of the pulmonary arterial mean pressure during exercise to a) diastolic descent rate b) MVA op and c) MVA Gorlin The same group of patients as in fig 43

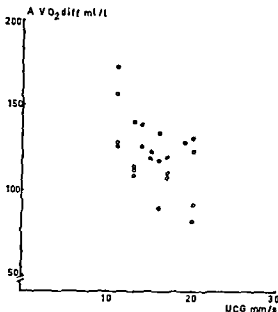

Fig 44 *The relation of the arterio venous oxygen difference during exercise to the diastolic descent rate in patients with atrial fibrillation*

Pulmonary arterial pressure In the material of all patients with atrial fibrillation (table 24) this pressure at rest showed a probably significant inverse relationship to the descent rate and MVA op During exercise the former relation was probably significant and the latter significant

In the selected material of table 25 the correlation between the mean pressure during exercise and the descent rate was still probably significant while the relationship to the two other variables was not significant Fig 45 shows the relation between the mean pulmonary arterial pressure during exercise and the three variables in these patients Four patients had pressures exceeding 75 mm Hg, of these three had descent rates between 10 and 11 mm/s and MVA op between 1 0 and 1 3 cm² The fourth patient case 85, had both a higher descent rate and a larger MVA op, 1 8 cm² however he showed the highest oxygen consumption 1300 ml/min, and cardiac output, 10 9 l/min, during exercise

Pulmonary arterial wedge pressure Inverse relationships were found to all the three variables, none, however, was statistically significant

Fig 46 shows the relation between the wedge pressure during exercise and the three variables in the patients of the selected material Though not statistically significant the best correlation was to MVA op the patient with the highest wedge pressure had an area of 1 1 cm², the one with the lowest pressure an area of 2 5 cm² Three patients with the lowest descent rates, 10—11 mm/s had MVA op of 1 1—1 3 cm² and wedge pressures during exercise between 44 and 60 mm Hg However, the mentioned patient with the lowest pressure and large area had a descent rate of only 16 mm/s

Right atrial pressure A significant inverse relationship was found to the Gorlin area, this was caused by two patients with elevated pressures and small areas, 0 4 and 0 6 cm², and a pressure of 0 mm Hg in a patient with a relatively large area, 1 4 cm²

Vascular resistance

Systemic vascular resistance The resistance during exercise showed a probably significant negative correlation to descent rate and to Gorlin area, table 25

Pulmonary vascular resistance The resistance at rest was significantly correlated to both descent rate and MVA op in the whole material of patients with atrial fibrillation table 24 the values calculated on exercise data were also significantly related to MVA op and probably significantly to descent rate In the selected material, table 25 the latter correlation was significant

The resistance was above 6 units during exercise in three patients of all those with atrial fibrillation these patients had low descent rates, 10—11 mm/s, and small MVA op 0 9—1 1

cm². Five patients had values below 1.5 units at descent rates between 11 and 20 mm/s and at MVA op. of 1.3–2.5 cm².

DISCUSSION

In the present study no significant correlations were found between cardiac output and mean pulmonary arterial and wedge pressures at rest and during exercise. These findings are partly at variance with those of WADE and BISHOP (92) who in patients with sinus rhythm found a small but significant inverse relationship between pulmonary arterial pressure and cardiac index at rest and a significant coefficient of correlation ($r = -0.44$) during exercise.

This discrepancy in results might be caused by different composition of the materials, more patients with high pulmonary arterial pressures being included in that of WADE and BISHOP.

BISHOP and WADE (8) did not find any significant correlation between pulmonary arterial wedge pressure and cardiac index at rest in patients with sinus rhythm; in patients with atrial fibrillation they only found a probably significant correlation in those of group III A.

The pulmonary arterial pressure showed a highly significant relationship to the wedge pressure in the present study; coefficients of correlation of the same order at rest were found by BISHOP and WADE (8).

If the alterations of pressures and flow in mitral stenosis were solely determined by the degree of mechanical obstruction caused by the decreased area of the mitral valve many correlations between this area and the hemodynamic parameters should be highly significant. However several mechanisms tend to modify this relation between the anatomical obstruction and the hemodynamics. WOOD (97) considered the behaviour of the pulmonary vascular resistance to be the most important physiological event in mitral stenosis. As shown by WOOD (97), among others, this mechanism is of importance especially in tight stenosis. — Pressure receptors in the left atrium or in the pulmonary veins have been postulated as a regulatory mechanism for the cardiac output and thereby for the pressure in the left atrium, e.g. ARAUJO and LUKAS (3) and HUGENHOLTZ et al. (56).

CARMAN and LANGE (16) emphasized the "variant hemodynamic patterns in mitral stenosis". Of 84 patients with predominant mitral stenosis with the same area of the orifice at operation, i.e. about 1 cm², 11 showed hemodynamic findings which differed from the usual pattern. Four patients, of whom two had sinus rhythm, had normal pressures in the pulmonary circulation and a low cardiac index at rest and after mild exercise. Seven patients had a normal cardiac index at rest and during exercise. To explain the hemodynamics in the first four cases they discussed an adaptive mechanism inverse to that seen in trained athletes.

Atrial fibrillation implies a further modification of the hemodynamics in mitral stenosis through the reduction of the cardiac output. The myocardial factor with its consequences for the hemodynamics is also likely to be of greater importance in this rhythm, e.g. FLEMING and WOOD (41).

Thus it is not surprising that the correlations between several hemodynamic parameters and the mitral valve area were of low or no statistical significance. Fewer significant correlations were also found in patients with atrial fibrillation than in those with sinus rhythm.

The agreement between the area estimated at operation and that calculated by the Gorlin formula with regard to their relationships to the different parameters was also better in patients

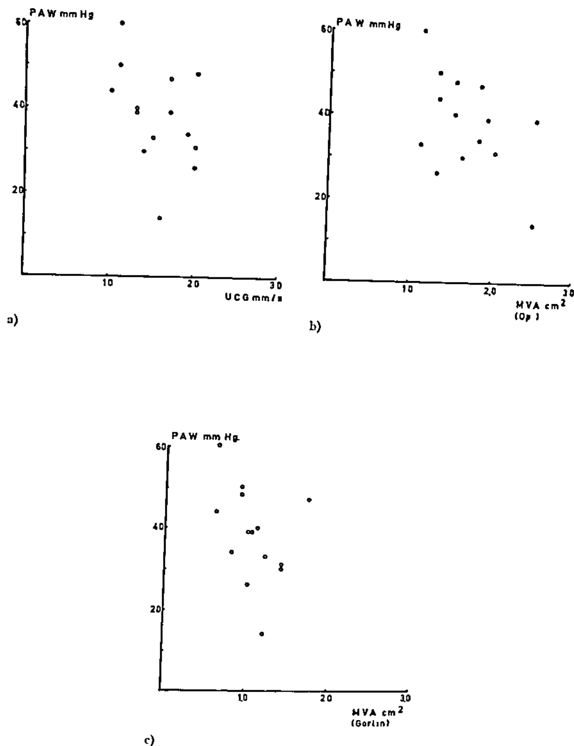

Fig 46 *The relation of the pulmonary arterial wedge pressure during exercise to a) descent rate of UCG b) MVA op and c) MVA Gorlin The same group of patients as in fig 43*

at rest in relation to the calculated valve area agree also well with the relation between the left atrial pressure and the valve area in the studies of DICKENS et al (18) and HUGENHOLTZ et al (56) pressures above 20 mm Hg were only seen in patients with an area less than 1 5 cm² The size of the mitral valve area estimated by the surgeon at these pressures was 1 6 cm² or smaller and the corresponding de cent rate 15 mm/s or lower Thus the three methods of estimating the stenosis showed a good agreement

Case 135 had low pulmonary arterial and wedge pressures during exercise though the stenosis found at the opera tion was of significant degree The hemodynamic response to exerci e in this patient resembles that described by CARMAN and LANGE (16) in their group A in which the patients also had low pressures during exercise though the steno is was significant The UCG finding 20 mm/s in this patient was more closely related to the surgical findings than the valve area of 2 6 cm² calculated by the Gorlin formula

In the patients with atrial fibrillation the pres ures in the pulmonary circula tion also showed an inverse relationship to the three variables but the variation in pres ure at a certain area or descent rate was greater than in sinus rhythm However the smallest areas and the lowest de cent rates corre ponded to the highest pulmonary arterial pressure

This relation to pulmonary arterial pre sure was reflected in the inverse relationship to the pulmonary vascular resistance which was caused by high resistance values with the smallest valve areas and lowest de cent rates These findings are consistent with those of ARAUJO and LUKAS (3) and DICKENS et al (18) who found the highest resistance values with the smallest calculated valve areas otherwise they found a poor correlation between resist ance and valve area In the present series the resistance values during exer cise in the patients with atrial fibrillation also varied from normal, 1 2 units, to very high values, 9 3 units, in surgically estimated areas between 0 9 and 1 3 cm²

The highest pulmonary vascular re sistance in the patients with sinus rhythm was 6 9 units in case 75 As discussed in chapter VI this patient illustrates that the mitral valve area estimated by the surgeon, 2 1 cm², is not equal to the degree of functional obstruction when the leaflet changes are advanced with calcifications and de creased mobility The low rate of descent in the UCG tracing, 7 mm/s, corre sponded well to the alteration in hemodynamics, the low maximal ampli tude predicted that the advanced leaflet changes were unfavourable for a good result of the valvulotomy

SUMMARY

Three methods which were used in the present study to evaluate the degree of mitral steno is the descent rate of the UCG tracing, the mitral valve area calculated by the Gorlin formula and the valve area estimated at operation, were correlated to some clinical data and to hemodynamic findings Patients with sinus rhythm and with atrial fibrillation were studied separately

Besides these some other correlations between the hemodynamic parameters were performed No significant correla tions were found between the cardiac output at rest and during exercise and the mean pressures in the systemic and pulmonary circulations The pulmonary arterial mean pressure showed a highly significant correlation to the pulmonary arterial wedge pressure at rest and during exercise in both heart rhythms

The three variables descent rate

with sinus rhythm, a not unexpected finding owing to their mutual relations in the two rhythms studied in chapter VII

On the whole the three variables, descent rate, areas estimated at operation and calculated by the Gorlin formula, agreed in their relationship to the different parameters The trend in the correlations generally was the same even if differences in the level of statistical significance were found

The cardiac index at rest showed a positive significant or probably significant relationship to the three variables in patients with sinus rhythm The correlation was strongest to the Gorlin formula, an expected finding since the mitral valve flow is an integral part of the formula

ARAUJO and LUKAS (3) related the cardiac index to the calculated area and found indices between 3 0 and 3 5 l/min/m² with areas between 1 6 and 0 9 cm², below this area the cardiac index declined directly In the present series most indices below 3 0 l/min/m² were found in patients with calculated *areas smaller than 1 5 cm², in those with* surgically estimated areas smaller than 2 0 cm² and descent-rates below 20 mm/s This distribution of cardiac indices in relation to calculated valve *areas corresponds fairly well to the* series of HUGENHOLTZ et al (56) in which the cardiac index was determined by a dye technique and the mitral valve area calculated on the basis of data from left heart catheterization A significant correlation was found, $r = 0\ 41$, between the index and the area in their material of 24 patients with sinus rhythm and 20 with atrial fibrillation Of the patients with sinus rhythm 11 had a cardiac index below 3 0 l/min/m², 10 of these had an area of 1 5 cm² or less

In the patients with *atrial fibrillation* of the present series the cardiac index (BSP) at rest showed a stronger correla*tion to MVA op* than to the other variables, however, none was sta cally significant The weak relation between cardiac output and the de of mitral valve obstruction in pati with *atrial fibrillation* has been discu in chapter V

The inability of the heart to keep an adequate output ought to bec more apparent during exercise Howe the cardiac index *during exercise did* show any significant correlation to three variables in patients with si rhythm and only a probably signific correlation to the Gorlin area in th with atrial fibrillation However, in patients with sinus rhythm and most advanced degree of stenosis, c 104 and 138, no exercise test could performed The quite inadequate blo flow during exercise in patients w atrial fibrillation and the most advan stenosis was reflected in the inver *probably significant, relationship of* arterio venous oxygen difference to t three variables In patients with sin rhythm only low negative coefficien of correlation were found for t *corresponding relations*

The strongest correlations were fou between the pressures in the pulmona circulation and the three variables patients with sinus rhythm The Gorl *area even in this respect* showed th highest coefficients of correlation, whic was expected since the wedge pressu is used in the denominator of th formula

HUGENHOLTZ et al (56) found highly significant relationship of th calculated valve area to the left atria pressure, $r = -0\ 618$, as well as to th left ventricular filling pressure gradient $r = -0\ 708$ These coefficients of cor relation were of the same order as *tho* found for the relation between the pulmonary arterial wedge pressure and the calculated area in the present study The distribution of the wedge pressures

GENERAL SUMMARY AND CONCLUSIONS

The purpose of the present investigation was to study the place of the ultrasoundcardiogram (UCG) in the preoperative evaluation of patients with mitral valvular disease In addition a methodological study of UCG was performed

In the *methodological study* (chapter III) it was shown that measurements of the diastolic descent rate of the UCG during 10 heart cycles and of the maximal amplitude during 5 heart cycles provide a determination of the two variables in each UCG tracing that is sufficiently accurate for clinical use The method showed a good reproducibility in duplicate recordings and in recordings performed on different days The most important cause for the variation of the UCG findings was the site on the chest wall from which the recording was performed The diastolic descent rate showed no significant difference between recordings performed during atrial fibrillation and during sinus rhythm in the same patients The influence of the respiratory movements upon the UCG tracing was also studied

In a series of 71 patients with predominant mitral stenosis the *UCG findings were related to clinical hemodynamic and surgical findings*

1 *Clinical findings* The functional disability of the patients was assessed by a modification of the criteria of the New York Heart Association (chapter IV) The descent rate of UCG was highest in the group with the least disability

The clinical groups were also compared with respect to hemodynamic findings and to mitral valve areas estimated by Gorlin's formula and at operation

2 *Hemodynamic findings* Patients with descent rates of ≤ 15 mm/s and > 15 mm/s were compared (chapter V) In those with sinus rhythm the mean values of pulmonary arterial and pulmonary arterial wedge pressures at rest and during exercise were significantly higher in the group with the lower descent rate In the patients with atrial fibrillation the differences between the mean values of the two groups showed the same trend but they were not statistically significant Patients belonging to the same group of descent rate but with different heart rhythms were also compared those with atrial fibrillation had significantly lower cardiac output and higher arterio venous oxygen difference than patients with sinus rhythm

The *mitral valve area* calculated on the basis of hemodynamic data showed a statistically significant correlation to the descent rate of UCG in the patients with sinus rhythm but not in those with atrial fibrillation (chapter VII)

3 *Surgical findings* The mitral valve area was determined in square centimeters by a method which showed a relatively good reproducibility (chapter I)

calculated, and surgically estimated, valve areas, showed good agreement in the relationships to the hemodynamic parameters, only small differences in the level of statistical significance were found

Cardiac index (BSP) at rest showed a significant or probably significant correlation to the three variables in patients with sinus rhythm while no significant correlation was found in patients with atrial fibrillation

The arterio-venous oxygen difference was probably significantly correlated to the three variables at rest in sinus rhythm and during exercise in atrial fibrillation

The pulmonary arterial wedge pressure at rest and during exercise showed a significant or highly significant inverse relationship to the three variables in patients with sinus rhythm but not in those with atrial fibrillation

The pulmonary arterial mean pressure showed fundamentally the same correlations as the wedge pressure in patients with sinus rhythm In patients with atrial fibrillation it was generally more closely related to the three variables than the wedge pressure

The calculated pulmonary vascular resistance showed an inverse relationship of variable statistical significance to descent rates and valve areas in both heart rhythms The highest resistance values were found in the patients with the smallest valve areas and lowest descent rates Normal resistance values were found both with small and large areas

On the whole the study of the correlation between the hemodynamics and the UCG-findings confirms that a descent rate of 15 mm/s or less represents an advanced mitral stenosis in patients with sinus rhythm Those with a descent rate of about 10 mm/s and a maximal amplitude exceeding 15 mm have signs of a very tight stenosis irrespective of the heart rhythm The patients with sinus rhythm and a descent rate within the range 20—27 mm/s generally showed signs of a less advanced stenosis even if the pressures in the pulmonary circulation were higher than normal during exercise

GENERAL SUMMARY AND CONCLUSIONS

The purpo e of the present investiga tion was to study the place of the ultrasoundcardiogram (UCG) in the preoperative evaluation of patients with mitral valvular disease In addition a methodological study of UCG was performed

In the *methodological study* (chapter III) it was shown that measurements of the diastolic descent rate of the UCG during 10 heart cycles and of the max imal amplitude during 5 heart cycles provide a determination of the two variables in each UCG tracing that is sufficiently accurate for clinical use The method showed a good reproducibility in duplicate recordings and in recordings performed on different days The most important cau e for the variation of the UCG findings was the site on the chest wall from which the recording was performed The dia tolic descent rate showed no significant difference between recordings performed during atrial fibril lation and during sinus rhythm in the same patients The influence of the re piratory movements upon the UCG-tracing was also tudied

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1 *Clinical findings* The functional dis ability of the patients was a se ed by a modification of the criteria of the New York Heart As ociation (chapter IV) The descent rate of UCG was highest in the group with the least disability

The clinical groups were also compared with respect to hemodynamic findings and to mitral valve areas estimated by Gorlin's formula and at operation

2 *Hemodynamic findings* Patients with descent rates of ≤ 15 mm/s and > 15 mm/s were compared (chapter V) In those with sinus rhythm the mean values of pulmonary arterial and pul monary arterial wedge pressures at rest and during exercise were significantly higher in the group with the lower descent rate In the patients with atrial fibrillation the differences between the mean values of the two groups howed the same trend but they were not statistically significant Patients belonging to the same group of descent rate but with different heart rhythms were also compared those with atrial fibrilla tion had significantly lower cardiac output and higher arterio venous oxygen difference than patients with sinus rhythm

The *mitral valve area* calculated on the basis of hemodynamic data showed a statistically significant correlation to the descent rate of UCG in the patients with sinus rhythm but not in those with atrial fibrillation (chapter VII)

3 *Surgical findings* The mitral valve area was determined in square centi meters by a method which showed a relatively good reproducibility (chap ter I)

The descent rate of UCG showed a highly significant correlation to the mitral valve area in the whole material (chapter VI) This correlation was poor in patients with an UCG-tracing of low maximal amplitude ($\leq$ 15 mm) The best correlation between descent rate and valve area was found in patients with sinus rhythm

The maximal amplitude of UCG was related to the mobility of the anterior mitral leaflet and to the degree of calcification of the mitral valve patients with an UCG tracing of low amplitude often had a mitral valve with restricted mobility of the anterior leaflet and advanced calcifications By analysis of variance these relationships were shown to be statistically highly significant

The origin and significance of the UCG tracing in relation to the movements of the anterior mitral leaflet studied by angiocardiography in different anatomical types of mitral stenosis is discussed in chapter VI The slow descent rate is postulated to be mainly caused by the narrowing of the mitral orifice in patients with a thin and pliable anterior leaflet in contrast to those with an immobile and calcified valve where it may be mainly caused by the rigidity of the leaflet

4 The accuracy of the UCG and of the mitral valve area calculated by the Gorlin formula, in predicting the valve area found at operation was compared (chapter VII) It was concluded that the former method is probably slightly better for predicting the degree of mitral stenosis

5 Finally, the descent rate of UCG, the calculated mitral valve area and the valve area estimated by the surgeon were correlated to hemodynamic data obtained by right heart catheterization (chapter VIII) The coefficients of correlation for the three estimates of the degree of mitral stenosis were on the whole of the same order

CONCLUSIONS

On the basis of the results of the present study it can be concluded that ultrasoundcardiography is a method showing a good reproducibility The diastolic descent rate of the UCG gives valuable information about the degree of mitral stenosis, especially in patients with sinus rhythm A pre operative UCG can often replace more time consuming and, for the patient, more inconvenient methods such as heart catheterization In order to calculate the pulmonary vascular resistance, which among other things is of importance for planning of the postoperative care, hemodynamic studies may be indicated in cases with a very low descent rate, about 10 mm/s, these patients often have an elevated resistance irrespective of the heart rhythm

If a hemodynamic study is considered necessary to estimate the degree of mitral stenosis in patients with atrial fibrillation it should be performed as a combined left and right heart catheterization The results of the present study show that the calculation of the mitral valve area solely on the basis of data obtained by right heart catheterization gives an inaccurate estimate of the degree of stenosis in patients with atrial fibrillation

The maximal amplitude of the UCG-tracing gives an idea of the condition of the anterior mitral leaflet which can be of value in the selection of patients with mitral stenosis for open heart surgery

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APPENDIX

Work test (heart rate beats/min) Work load (kpm/min) ♀ 200 / ♂ 300	400 / 600	600 / 900	UCG Descent rate (mm/s)	UCG Maximal amplitude (mm)	Gorlin formula Mitral valve area (cm²)	Operative findings Mitral valve area (cm²)	Mitral insufficiency Pre valvulotomy	Mitral insufficiency Post valvulotomy	Mobility of anterior leaflet	Degree of calcification	Cine fluorography (calcification)
106	—	—	18	23	—	2 4	0	0	(+++)	(+)	(+)
140	158	—	14	20	1 1	1 5	0	0	(+++)	0	0
120	—	—	15	25	1 1	1 6	0	0	(+++)	0	0
125	156	—	14	23	—	1 0	0	(+++)	(++)	(+)	0
142	175	—	27	22	3 4	2 1	0	0	(+++)	0	0
140	168	—	21	27	—	1 8	0	0	(+++)	0	0
141	163	—	20	21	2 1	1 7	0	(++)	(+++)	0	0
160	—	—	11	20	0 8	1 0	0	(++)	(+++)	0	0
138	168	—	16	22	1 5	1 7	0	0	(+++)	0	0
120	158	—	15	21	1 4	1 5	0	0	(+++)	0	(+ ?)
108	144	(173)	19	22	2 4	2 9	0	0	(+++)	0	0
108	(129)	—	17	20	1 9	2 0	(+)	(+)	(++)	0	0
150	—	—	12	17	1 1	1 6	0	(+)	(++)	(++)	(+)
144	—	—	26	20	2 1	2 5	(+)	0	(+++)	0	0
105	144	—	19	17	1 2	2 0	0	0	(++)	0	0
108	153	(180)	20	22	2 1	2 3	(+)	0	(++)	0	0
134	—	—	19	22	1 9	2 1	(+)	(++)	(+++)	0	0
88	—	—	13	19	1 4	1 8	0	0	(+++)	0	0
92	155	—	17	18	1 0	2.4	(+)	(++)	(+++)	0	0
158	1 0	—	16	28	1 5	1 6	(+)	(++)	(+++)	0	0
86	137	—	8	20	1 2	1 1	(+)	(++)	(+++)	0	0
132	158	—	20	25	2.6	1 6	0	0	(+++)	0	0
109	148	—	10	16	1 1	0 9	0	0	(++)	(+++)	(+)
144	—	—	20	21	1 3	1 6	0	(+)	(+++)	0	0
114	(154)	—	[illegible]6	24	1 5	1 9	0	0	(+++)	0	0
100	(130)	—	[illegible]2	20	2.2	2 5	0	(++)	(+++)	(++)	(+)
91	114	(160)	13	15	2.2	1 9	(+)	(+)	(++)	(+++)	(+)

Table I A *Some data on patients with sinus rhythm*

Preoperative diagnosis MS = mitral stenosis, ReMS = restenosis mi = mitral insufficiency as = aortic stenosis, ai = aortic insufficiency, H = arterial hypertension *Work test* figures within brackets represent heart rate during work not performed in a steady state *Operative findings* for 0 — (+++) see methods *Cinefluorography* (+) calcification observed, 0 = no calcification

Case No	Sex	Age (years)	Height (cm)	Weight (kg)	Preoperative diagnosis	Clin group	Duration (years) to operation from Rheum fever	Onset of symptoms	Heart volume (ml)
1	F	61	154	64	MS mi	III A	—	6	860
79	F	42	168	64	MS ai	III A	30	2	750
90	F	42	166	54	MS	III A	22	14	790
95	F	30	172	68	MS ai	II	—	3	1050
96	F	29	154	48	MS mi	II	18	10	645
99	M	42	175	70	MS as ai	II	—	0	1100
100	F	42	155	57	MS	II	—	17	660
104	F	38	161	46	MS as ai	III A	29	5	760
105	F	30	159	63	MS as ai	III A	—	—	690
108	M	30	180	69	MS	III A	—	3	1050
109	M	49	170	63	MS	I	40	13	910
111	M	33	181	69	MS mi	II	32	16	1130
112	F	39	160	53	MS	III A	26	2	710
113	F	55	165	71	MS mi	III B	—	2	910
118	F	48	167	53	MS	II	—	5	745
121	M	45	173	69	MS mi	II	30	1	940
124	F	31	158	56	MS mi	II	21	2	640
126	F	57	159	48	MS mi	III A	—	5	830
129	F	54	158	59	MS mi	III A	40	—	1130
130	F	33	169	59	MS mi ai	II	—	6	940
131	M	39	172	60	MS	III A	11	3	800
135	F	38	165	47	MS mi	II	—	2	780
138	M	42	173	63	MS ai	II	—	4	1000
140	F	50	158	52	MS H	III B	—	3	760
143	F	44	160	50	MS	III A	26	5	940
149	M	57	173	74	MS mi	II	28	1	1350
152	M	48	188	99	MS mi	II	24	2	1350

Work test (heart rate beats/min) Work load (kpm/min) ♀ 200 ♂ 300	400 600	600 900	UCG Descent rate (mm/s)	UCG Maximal amplitude (mm)	Gorlin formula Mitral valve area (cm²)	Operative findings Mitral valve area (cm²)	Operative findings Mitral insufficiency Pre valvulotomy	Operative findings Mitral insufficiency Post valvulotomy	Operative findings Mobility of anterior leaflet	Operative findings Degree of calcification	Cine fluorography (calcification)
122	(154)	—	7	13	—	2 1	(++)	0	(+)	(+++)	(+)
100	—	—	12	15	—	1 1	(++)	(++)	(+)	(+++)	(+)
108	140	173	26	24	—	2 6	(++)	(++)	(+++)	0	0
84	138	(160)	10	13	—	1 7	(++)	(+++)	(+)	(+++)	(+)
86	140	—	11	18	—	1 4	(++)	(++)	(++)	(+)	0
83	117	(150)	20	23	—	2 0	(+++)	(+)	(+++)	(++)	(+)
123	145	157	23	20	—	2 4	(+++)	(+++)	(+++)	0	0
126	—	—	10	16	—	1 1	(++)	(++)	(+)	(+++)	(+)
106	142	—	18	19	—	1 9	(++)	(+)	(++)	0	0
94	132	—	11	10	—	2 0	(+++)	(+++)	0	(+++)	(+)
103	(157)	—	23	16	—	2 1	(+++)	(++)	(+++)	(+++)	(+)
113	133	155	23	20	—	1 8	(+++)	(+++)	(+++)	(++)	(+)

(Table I A continued)

Case No	Sex	Age (years)	Height (cm)	Weight (kg)	Preoperative diagnosis	Clin group	Duration (year) to operation from: Rheum fever	Duration (year) to operation from: Onset of symptoms	Heart volume (ml)
75	M	47	177	80	MS mi ai	III A	45	6	1420
97	M	46	174	59	MS mi	II	40	1	1080
101	F	52	160	56	MS mi	II	—	3	980
102	M	51	176	73	MS mi H	II	36	2	1250
123	M	59	166	65	MS mi	II	27	6	1040
132	M	37	179	72	MS mi	I	31	0	1000
136	F	34	160	56	MS mi	II	23	7	800
142	F	46	167	63	MS mi ai	III B	18	14	880
148	F	52	164	61	MS mi as	II	37	—	940
150	M	54	173	80	MS mi as ai	II	37	2	1420
156	M	43	173	80	MS mi	II	33	1	1120
158	F	42	168	59	MS mi	I	24	0	940

Work test (heart rate beats/min) Work load (kpm/min) ♀ 200 / ♂ 300	400 / 600	600 / 900	UCG Descent rate (mm/)	Maximal amplitude (mm)	Gorlin formula Mitral valve area (cm²)	Operative findings Mitral valve area (cm²)	Mitral insufficiency Pre-valvulotomy	Mitral insufficiency Post valvulotomy	Mobility of anterior leaflet	Degree of calcification	Cine fluorography (calcification)
(140)	—	—	22	23	—	1 7	0	0	(+++)	0	0
112	128	—	11	15	1.3	2 5	(+)	(+)	0	(+++)	(±)
106	—	—	17	24	1 0	1 9	0	(+)	(+)	0	0
88	—	—	13	13	—	2 0	0	(++)	0	0	0
152	—	—	17	21	1 7	1 8	0	0	0	0	(+)
146	—		16	23	1 5	1 8	0	0	(+++)	0	0
98	—	—	20	25	1 4	2 0	0	0	(++)	0	0
(163)	—	—	14	12	1 1	1 9	0	0	0	(+++)	(+)
120	—	—	10	19	0 6	1 3	0	0	(+)	0	0
136	—	—	16	22	1 2	2 5	0	0	(+++)	0	0
152	—	—	20	21	0 9	1 5	0	0	(+)	0	0
115	—	—	19	24	0 8	1 8	0	(+)	(+)	0	0
142	—	—	11	14	0 8	0 9	0	0	(±)	(+++)	(+)
148	—	—	21	23	—	2 3	0	0	(++)	0	0
—	—	—	11	28	0 6	1 1	0	0	(++)	(±)	0
77	136	—	13	21	1 0	2 5	0	0	(+++)	(+)	(+)
162	—	—	14	24	1 4	1 6	0	0	(+++)	0	0
100	—	—	17	19	0 4	1 4	0	(++)	(+++)	0	0
144	—	—	11	21	0 9	1 3	0	(++)	(++)	(+)	0
163	—	—	13	24	1 1	1 5	0	0	(++)	0	0
121	—	—	20	24	1 0	1 3	(±)	?	(++)	0	0
104	129	—	15	23	1 2	1 1	0	(+)	(++)	0	0
159	—	—	19	19	—	1 6	0	(+)	(+)	0	0
118	—		10	14	0 9	1 6	(±)	(+)	(++)	(+++)	(+)
160	—	—	17	21	—	1 5	0	(+++)	(++)	0	0
140	—	—	17	23	—	2 3	(+++)	(+++)	(+)	0	0
(150)			11	20	—	1 1	(+++)	(+++)	(+)	(+++)	(+)
158	—		15	1	—	1 5	(++)	(+++)	(+)	0	0
15		—	16	14	—	1 7	(+++)	(++)	(+)	(+)	0
(160)		—	16	19	—	2 0	(+++)	(+++)	(++)	0	0
87		—	20	15	—	1 8	(++)	(++)	(+++)	(++)	(+)
148	150		13	18	—	1 1	(++)	(++)	(++)	(++−)	(+)

Table I B *Some data on patients with atrial fibrillation Symbols as in table I A*

Case No	Sex	Age (years)	Height (cm)	Weight (kg)	Preoperative diagnosis	Clin group	Duration (years) to operation from Rheum fever	Onset of symptoms	Onset of fibrillation	Heart volume (ml)
39	F	37	158	61	MS mi	III B	—	11	[illegible]	980
81	M	40	175	83	MS mi	III A	—	3	3	12[illegible]0
83	F	46	162	71	MS	III A	23	21	[illegible]	910
84	M	54	175	70	MS mi as ai H	III B	36	20	20	1680
85	M	42	171	66	MS mi	III A	—	1	1	1325
87	F	48	160	55	Re MS	II	—	14	[illegible]	925
88	F	39	168	68	MS mi ai	II	24	17	1	1030
89	M	60	170	61	MS mi	III B	59	—	1	1450
91	F	43	164	63	MS	III A	5	20	4	1340
92	M	52	176	82	MS	III A	—	1	1	1250
106	F	43	169	65	MS	III A	24	20	0	1090
107	M	56	165	51	Re MS as	III B	35	18	16	950
116	M	57	173	74	Re MS	III B	45	15	9	1490
117	F	56	169	70	MS ai	III B	43	16	2	1580
119	M	47	171	63	MS	III B	36	23	6	1500
120	F	52	167	78	MS mi H	III B	—	10	[illegible]	1750
125	M	49	167	51	MS	III A	34	2	2	825
127	F	53	165	58	Re MS mi	III B	34	19	6	1050
128	F	55	164	58	MS	III A	—	20	[illegible]	1210
133	F	58	164	66	MS	III A	—	11	1	1120
139	M	55	175	56	MS mi	II	16	1	1	740
144	M	48	172	76	MS mi	III A	—	—	[illegible]	1500
145	F	59	171	52	MS	III A	—	10	10	680
155	F	51	165	65	MS	III A		19		1050
157	F	42	163	69	MS	III A	—	8	8	1350
57	F	51	1[illegible]0	62	MS mi	III A	34	11	2	1380
73	M	41	165	55	MS mi	III B	—	10	5	1660
98	F	60	164	63	MS mi ai H	III A	43	38	6	1100
110	F	57	150	58	MS mi as	III A	48	[illegible]3	11	1320
122	F	12	157	57	MS mi ai	III B	34	6	1	950
146	F	53	171	59	MS mi as ai	III B	41	30	5	1190
153	M	52	1[illegible]3	78	MS mi	III A	38	20	6	1650

109 R	8	1 0	9 8	140	11	2 6	7 0	19 4	91 8	80 0	23	119	76	97	16	19	30	17	—	8 3	1 1	2 3
F	119	10 5	12 7	88	107	983	27 4	19 8	88 3	41 0	91	171	88	118	66	32	50	30	0	11 3	1 9	2 5
111 R	61	9 6	7 4	150	116	403	10 2	19 1	96 1	74 5	42	116	59	82	36	17	21	16	1	8 6	0 8	2 4
F	110	10 8	14 4	98	131	900	22 6	19 6	93 3	50 3	84	162	70	99	67	35	50	38	0	9 1	1 1	1 4
112 R	108	3 5	4 4	37	41	162	7 4	18 2	93 1	67 7	46	125	64	91	47	26	35	29	0	26 0	1 7	0 8
F	1 8	8 2	6 2	46	35	1013	31 2	17 8	89 8	20 7	123	116	86	100	110	58	71	45	—	12 2	3 2	1 3
113 R	148	6 7	7 0	65	73	469	5 7	18 8	91 9	70 8	40	151	83	115	31	15	22	13	—	17 2	1 3	2 5
F	149	7 2	8 3	60	63	861	15 9	19 4	89 3	31 9	112	180	88	126	61	33	45	38	1	16 3	0 9	1 7
118 R	66	3 7	4 1	56	62	211	7 1	17 0	91 1	60 5	57	142	66	96	30	15	20	15	3	26 0	1 4	1 0
F	123	7 8	8 9	63	72	612	21 9	17 4	87 3	40 4	82	171	76	118	69	38	52	41	8	15 1	1 4	1 4
121 R	78	6 4	7 6	82	97	269	9 3	20 2	97 6	76 8	12	121	78	100	25	8	16	12	0	15 6	0 6	2 2
F	116	8 4	10 3	72	83	910	20 6	20 6	98 7	46 2	108	155	91	120	48	25	36	25	0	14 3	1 3	1 9
124 R	77	5 2	4 5	68	58	219	5 7	19 0	99 3	77 1	42	120	68	90	30	8	17	11	—2	17 3	1 2	1 7
F	111	8 5	7 4	77	67	710	17 6	19 8	96 1	52 3	87	138	65	93	18	23	31	21	—2	10 9	1 2	2 0
126 R	56	5 1	4 2	91	75	205	4 9	14 7	100 2	73 1	40	143	71	102	40	14	25	16	1	20 0	1 8	1 2
F	120	9 0	7 7	75	64	976	32 9	18 6	93 1	34 6	109	164	72	99	68	36	53	42	5	11 0	1 2	1 5
129 R	46	4 2	5 6	55	74	201	5 1	19 0	96 1	71 1	48	141	76	107	40	16	27	18	0	25 4	2 1	1 0
F	115	8 6	9 2	75	80	754	19 1	19 6	85 6	40 5	08	—	—	—	51	29	14	33	0	—	1 3	—
130 R	99	5 9	6 2	60	63	252	6 3	18 2	98 7	75 1	43	141	71	93	41	11	26	20	0	15 7	1 0	1 4
F	146	9 2	9 1	63	63	767	20 7	18 9	99 0	55 2	83	170	81	110	70	38	53	46	4	12 0	0 8	1 6
131 R	44	4 9	4 1	112	93	211	9 0	19 0	98 6	72 7	49	135	73	92	46	19	28	22	0	18 8	1 2	0 8
F	107	8 9	7 2	83	67	746	22 0	18 2	95 7	49 0	85	147	80	98	88	45	65	52	3	11 0	1 5	1 5
135 R	63	4 2	4 0	67	64	181	4 4	17 2	90 9	66 1	43	100	55	74	21	6	12	6	0	17 6	1 4	3 2
F	95	6 7	(1	71	64	627	16 3	17 8	91 8	42 5	93	119	66	83	34	12	21	15	4	17 4	0 9	1 9
138 R	87	5 9	5 4	68	62	235	5 4	19 2	93 6	71 1	43	110	66	84	59	30	14	32	—	14 2	2 0	1 1
F	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
140 R	101	4 0	4 6	40	46	133	2 8	17 8	90 6	71 9	33	182	100	134	43	19	29	18	—	33 5	2 8	0 9
F	159	8 2	5 4	52	34	718	15 4	18 2	93 6	55 2	88	201	105	149	76	35	55	37	—	18 2	2 2	1 7
143 R	76	—	5 8	—	76	—	—	16 3	95 5	79 5	26	153	95	121	33	17	24	20	1	20 4	0 7	1 4
F	107	8 2	9 0	77	84	612	16 2	16 6	96 6	49 8	78	169	100	128	55	36	15	31	—	15 6	1 3	1 5

Table II A *Data from right heart catheterization on patients with sinus rhythm*

R = rest L = exercise S = systolic, D = diastolic M = mean PAW = pulmonary arterial wedge

Case No	Heart rate (beats/min)	Cardiac output (l/min) Fick	Cardiac output (l/min) BSP	Stroke volume (ml/beat) Fick	Stroke volume (ml/beat) BSP	Oxygen consumption (ml/min STPD)	Ventilation (l/min BTPS)	Oxygen capacity (ml/100 ml)	Oxygen saturation (%) arterial	Oxygen saturation (%) mixed venous	Art ven oxygen diff (ml/l)	Pressures (mm Hg) Brachial artery S	Brachial artery D	Brachial artery M	Pulmonary artery S	Pulmonary artery D	Pulmonary artery M	PAW M	R atr M	Calculated vascular resistance (units) Syst circ	Pulm circ	Mitral valve area (cm²) (Gorlin form.)
1 R	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
L	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
79 R	89	3 8	3 6	43	40	165	4 2	18 6	96 2	72 6	44	126	73	92	19	26	36	22	0	21 0	3 7	1 0
L	120	7 2	4 7	60	39	651	14 8	19 0	97 0	49 4	90	143	80	103	76	41	62	46	4	14 3	2 2	1 2
90 R	94	5 1	6 1	54	65	231	5 8	19 0	92 4	68 6	15	137	81	100	46	21	32	14	0	19 6	3 5	1 0
L	122	7 9	7 4	65	61	745	16 7	19 4	97 6	49 3	94	167	85	115	48	27	42	36	—	14 5	0 8	1 1
95 R	54	—	—	—	—	—	—	—	—	—	—	—	—	—	45	20	29	20	—	—	—	—
L	112	—	—	—	—	—	—	—	—	—	—	—	—	—	80	44	58	52	5	—	—	—
96 R	104	7 0	8 2	67	79	196	6 0	17 8	96 5	80 6	28	131	79	103	28	9	17	7	—	14 7	1 4	4 3
L	144	8 3	8 6	58	60	709	17 2	18 1	99 8	52 7	85	116	91	112	44	17	25	17	0	13 5	1 0	2 4
99 R	78	—	—	—	—	—	—	—	—	—	—	—	—	—	38	20	26	19	—	—	—	—
L	126	—	—	—	—	—	—	—	—	—	—	—	—	—	55	34	42	30	0	—	—	—
100 R	90	5 3	5 0	59	56	264	10 6	19 8	99 8	74 5	50	129	80	98	19	7	8	3	—	18 5	0 9	—
L	134	10 0	7 7	75	58	1063	26 5	20 2	98 8	46 4	106	—	—	—	41	29	34	28	0	—	0 6	2 1
104 R	113	—	4 0	—	35	—	—	16 3	83 1	52 3	50	116	69	90	84	34	56	29	—	22 5	6 8	0 8
L	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
105 R	100	4 7	4 0	47	40	271	9 0	17 0	98 6	64 4	58	122	66	96	33	13	20	15	—	20 4	1 1	1 2
L	132	9 6	6 4	73	48	781	18 2	17 4	95 1	48 4	81	162	74	110	62	34	49	38	3	11 9	1 1	1 8
108 R	84	6 4	7 8	76	93	315	9 2	21 7	92 4	69 9	49	145	76	100	57	35	47	32	5	15 6	2 3	1 0
L	124	10 3	11 8	83	95	1101	27 4	22 0	93 0	44 5	107	179	83	112	110	64	82	43	—	10 8	3 8	1 7

Table III Data from right heart catheterisation on patients with mitral ... [illegible]

R = rest; E = exercise; S = systolic; D = diastolic; M = mean; PAW = pulmonary arterial wedge

Case No.	Heart rate (beats/min)	Cardiac output (l/min)	Cardiac output Each BSI	Stroke volume (ml/beat)	Stroke volume Each BSI	Oxygen consumption (ml/min STPD)	Ventilation (l BTPS)	Oxygen capacity (vol/100 ml)	Oxygen saturation (%) arterial	Oxygen saturation (%) mixed venous	A-V oxygen diff (ml/l)	Brachial artery S	Brachial artery D	Brachial artery M	Pulmonary artery S	Pulmonary artery D	Pulmonary artery M	PAW M	R atr M	Calculated mitral valvular resistance (units) Syst	Calculated mitral valvular resistance (units) Diast	Valve area (cm²) (Gorlin formula)
39 R	6		0.0	—	66			20.7	90.8	66.7	50	—	—	17	6	11	9	1	—	0.4	—	
E	117	—	3.7		49				—	—	—		—	4	18	34	—	6	—	—	—	
81 R	26	3.2	3.4	123	120	921	8.2	20.2	95.3	67.7	0	10	68	85	21	8	12	8	2	26.6	1.3	1.2
E	33	.8	5.4	109	10?	710	17.9	20.5	100.5	38.0	178	140	85	115	36	16	21	20	6	19.8	0.7	1.3
83 R	57	4.9	3.8	86	67	235	6.7	17.8	98.6	71.4	48	127	68	85	47	21	32	23	—	17.3	1.8	0.9
E	8	6.0	5.4	77	65	6	18.?	18.6	96.7	37.6	110	138	77	103	78	36	56	39	14	17.2	2.8	1.0
84 R	64		3.8	—	59	—	—	2 5	92.3	16.1	54	203	108	146	46	21	31	20	2	38.1	2.9	—
E	94	7.4	5.4	79	57	87	1( )	20.8	91.9	42.2	109	—	—	—	83	34	57	47	4	—	1.4	—
8 R	84	—	—		—	—		20.5	94.4	64.2	62	131	78	101	71	41	54	32	—	—	—	—
E	1 1	10.9	—	64		113	1.3	21.2	94.4	3 0	121	119	71	73	103	47	8	47	17	7.9	1.6	1.7
87 R	72	4.4	3.2	61	44	216	5.0	17.7	90.9	63.4	49	146	106	120	34	14	23	22	—	27.2	2.5	1.5
E	104	6.5	5.4	63	39	589	13.9	18.4	91.6	41.5	91	168	108	139	55	31	37	—	4	21.4	—	—
88 R	8	5.7	6.5	73	83	301	15.1	19.0	98.9	71.3	53	130	75	95	33	14	21	17	—	16.7	0.7	1.3
E	117	8.8	9.0	79	60	607	18.5	19.0	99.0	50.8	92	165	73	102	48	25	37	31	6	9.1	0.7	1.5
89 R	86	3.6	3.2	42	37	259	11.4	19.2	97.7	60.5	79	135	81	109	41	26	34	31	—	30.3	0.8	—
E	120	6.0	4.5	50	38	759	20.8	19.4	91.0	29.1	126	118	83	100	85	47	58	43	10	16.2	2.5	1.1
91 R	77	—	3.5	—	45	257	5.5	—	—	—	—	130	90	110	63	30	46	31	—	31.4	4.3	0.7
E	17(	—	4.6	—	37	676	17.7	—	—	—	—	158	116	133	108	68	89	44	10	29.9	8.3	0.5
9? R	5	7.6	3.3	46	59	151	4.5	23.3	93.(	63.3	57	11?	73	89	21	8	13	8		35.2	1.9	1.2
E	75	4.6	5.?	41	6?	613	18.3	23.7	97.3	41.0	134	119	72	1 4	38	17	2(	14	6	29.(	2.(	1.1

Case No	Heart rate (beats/min)	Cardiac output (l/min) Fick	Cardiac output (l/min) BSP	Stroke volume (ml/beat) Fick	Stroke volume (ml/beat) BSP	Oxygen consumption (ml/min STPD)	Ventilation (l/min BTPS)	Oxygen capacity (ml/100 ml)	Oxygen saturation (%) arterial	Oxygen saturation (%) mixed venous	Art ven oxygen diff (ml/l)	Pressures (mm Hg) Brachial artery S	Brachial artery D	Brachial artery M	Pulmonary artery S	Pulmonary artery D	Pulmonary artery M	PAW M	R atr M	Calculated vascular resistance (units) Syst circ	Pulm circ	Mitral valve area (cm²) (Gorlin form.)
149 R	63	5 1	5 6	81	89	190	7 1	16 8	91 9	70 1	37	140	75	100	28	8	18	9	1	19 6	1 8	2 1
I	90	9 6	10 0	106	111	847	19 8	16 3	89 6	35 6	88	152	80	101	55	26	35	22	—	10 5	1 2	2 2
152 R	62	7 5	6 4	121	103	344	13 6	19 4	91 1	70 3	46	106	63	76	30	11	18	11	0	10 1	0 9	2 1
I	93	12 1	10 8	130	116	970	22 7	19 4	89 7	49 1	80	127	63	86	81	35	52	31	—	7 1	1 7	2 2
75 R	60	5 1	5 2	85	87	322	11 2	19 0	101 1	67 8	63	113	79	102	42	20	29	19	—	20 0	2 0	—
I	98	—	6 5	—	66	—	—	19 6	97 2	39 3	113	183	106	139	110	58	78	33	—	21 4	6 9	—
97 R	60	4 3	6 5	72	108	210	5 0	19 0	98 1	72 1	49	111	71	80	29	11	16	11	—	18 6	1 2	—
I	83	7 6	8 4	92	101	678	15 0	19 4	99 9	54 0	89	134	79	102	50	25	34	23	0	13 4	1 4	—
101 R	89	7 3	5 8	82	65	191	5 3	15 9	97 4	80 8	26	125	79	103	28	16	22	14	2	14 1	1 1	—
I	118	9 1	7 9	77	67	739	18 3	16 2	95 6	45 4	81	153	88	113	56	26	41	32	4	12 4	0 9	—
102 R	58	5 8	5 8	100	100	279	7 7	20 5	95 6	72 1	48	182	103	137	32	10	18	12	—	23 6	1 0	—
I	89	11 1	9 8	125	110	1111	31 4	20 5	87 3	38 3	100	204	110	151	72	32	50	29	4	13 6	1 9	—
123 R	58	4 1	4 5	70	78	222	5 9	18 4	97 2	68 1	54	124	71	91	35	17	25	18	0	22 2	1 7	—
I	94	7 9	8 8	84	94	982	27 8	19 2	98 6	34 0	124	144	79	109	76	45	60	51	11	13 8	1 1	—
132 R	18	—	5 0	—	104	281	7 9	—	—	—	—	123	63	88	22	6	13	10	2	17 6	0 6	—
I	78	10 8	8 9	138	114	885	20 2	19 0	98 0	55 3	82	153	72	99	43	18	24	18	3	9 2	0 6	—
136 R	76	5 0	5 9	66	78	171	4 9	15 5	93 8	71 7	34	122	73	93	25	9	16	9	0	18 6	1 4	—
I	105	10 1	10 3	96	98	636	14 0	15 3	94 8	53 5	63	127	69	99	37	17	24	16	2	9 8	0 8	—
142 R	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
I	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
148 R	55	—	5 0	—	91	213	4 9	—	—	—	—	103	52	72	30	9	17	11	0	14 4	1 2	—
I	98	8 7	8 4	89	86	617	14 6	16 8	93 2	50 9	71	126	62	88	62	28	42	29	2	11 3	1 5	—
150 R	58	5 5	6 3	95	109	210	6 8	16 1	100 0	72 8	41	110	57	78	40	15	26	19	0	14 2	1 2	—
I	91	9 4	10 7	103	117	770	18 1	17 8	94 2	48 4	82	138	67	95	86	34	55	34	0	10 1	2 2	—
156 R	61	4 6	6 9	71	106	222	6 5	19 3	97 8	72 9	48	132	75	99	41	15	25	8	1	21 5	3 8	—
I	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
158 R	63	7 8	5 5	121	87	241	5 2	16 6	92 4	73 8	31	124	72	93	35	12	21	12	2	11 9	1 5	—
I	105	10 9	9 2	104	88	677	13 7	16 9	92 7	56 0	62	153	81	110	62	27	42	22	4	11 1	1 8	—

	61	1		66		209	3	19 7	9 4	69 9	50	160	80	114	54	25	3)	21	3	27 1	1 3	0 9
1 R								—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
F						—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1 R						—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
F																						
R	5	3 2	3 9	5	71	158	5 6	18 9	91 9	68 2	50	131	56	83	29	14	18	13	—	25 9	1 6	—
F	125	54	5 9	4	17	609	14 0	20 0	97 8	43 5	108	165	84	109	58	33	44	33	11	19 5	1 9	—
3 R	113	3 5	3 1	31	27	278	10 (	20 5	82 8	43 6	80	116	94	109	95	56	75	—	—	31 1	—	—
F				—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
98 R	62	3 1	4 1	43	57	220	5 4	20 1	95 6	60 7	70	194	102	142	63	24	35	23	6	158	3 9	—
F	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
110 R	74	4 4	3 8	60	51	243	6 1	18 2	89 6	59 4	55	165	96	109	51	25	35	16	5	21 8	3 6	—
F	124	6 4	4 9	50	39	757	20 9	18 6	93 6	29 7	119	187	82	123	100	51	78	15	10	19 2	5 2	—
172 R	77	4 5	3 7	58	48	237	6 2	17 3	98 5	68 6	53	118	93	97	20	7	13	10	0	21 6	0 7	—
F	119	6 9	6 2	49	41	820	23 2	17 3	99 7	31 4	118	110	88	103	16	28	35	28	4	119	1 0	—
146 R	65	3 3	3 5	49	52	203	7 3	14 8	94 5	59 9	62	128	82	95	19	8	14	9	—	28 8	1 5	—
F	101	5 7	5 1	56	51	469	11 9	18 2	95 8	50 7	82	164	94	118	45	19	32	28	6	20 7	0 7	—
153 R	62	4 1	5 3	66	84	243	6 5	22 2	96 2	69 0	60	130	79	100	39	16	26	15	3	24 4	2 7	—
F	90	6	8 5	72	94	913	23 6	22 6	97 2	35 4	110	143	77	101	83	36	56	35	9	15 5	3 2	—

Case No	Heart rate (beats/min)	Cardiac output (l/min) Fick	Cardiac output (l/min) BSP	Stroke volume (ml/beat) Fick	Stroke volume (ml/beat) BSP	Oxygen consumption (ml/min STPD)	Ventilation (l/min BTPS)	Oxygen capacity (ml/100 ml)	Oxygen saturation (%) arterial	Oxygen saturation (%) mixed venous	Art ven oxygen diff (ml/l)	Pressures (mm Hg) Brachial artery S	Brachial artery D	Brachial artery M	Pulmonary artery S	Pulmonary artery D	Pulmonary artery M	PAW M	R atr M	Calculated vascular resistance (units) Syst circ	Calculated vascular resistance (units) Pulm circ	Mitral valve area (cm²) (Gorlin form.)
106 R	72	3.5	—	49	—	201	4.3	20.4	94.7	66.8	57	178	86	118	51	25	40	30	5	33.7	2.9	0.7
L	150	6.3	6.5	42	43	827	18.5	20.8	96.5	33.2	131	173	90	114	88	50	66	48	—	18.2	2.9	1.0
107 R	57	2.8	3.4	49	60	204	6.2	19.4	93.9	56.5	73	127	70	93	34	18	21	15	—	33.2	2.1	0.7
L	145	6.8	7.6	47	52	872	27.2	20.1	86.5	22.5	129	170	100	120	77	38	51	34	6	17.7	2.5	0.9
116 R	45	3.6	2.7	80	60	289	9.1	19.1	93.4	52.4	80	131	64	63	80	34	50	22	—	23.0	7.8	0.7
L	97	4.8	5.0	50	52	755	30.9	21.3	92.8	19.3	157	110	71	84	100	45	74	29	—	17.5	9.4	0.8
117 R	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
L	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
119 R	40	2.0	2.0	50	50	181	7.2	21.3	98.1	55.9	90	121	79	93	39	21	28	19	8	16.5	4.5	0.4
L	118	5.3	—	36	—	923	34.0	22.0	96.0	17.2	173	157	99	111	109	71	95	60	—	21.1	6.2	0.7
120 R	54	5.5	7.2	102	133	291	8.4	19.0	92.1	64.2	53	184	95	130	51	22	35	23	6	23.6	2.2	1.0
L	80	6.4	8.2	80	102	733	18.2	19.4	89.3	30.3	114	226	105	156	81	33	53	39	17	24.3	2.2	1.0
125 R	59	2.9	4.9	49	83	173	4.9	19.0	99.7	68.3	60	144	78	103	33	10	19	7	0	35.6	4.1	1.6
L	146	6.5	7.7	45	53	900	24.5	20.5	96.2	28.5	139	175	84	100	62	30	46	30	4	15.4	2.0	1.2
127 R	65	—	3.2	—	50	—	—	16.3	92.5	48.7	71	182	106	132	54	34	40	35	8	37.8	1.5	0.4
L	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
128 R	71	4.3	4.9	61	69	221	5.0	15.5	99.7	66.2	52	153	68	107	54	31	41	24	7	24.9	4.0	0.9
L	167	6.3	7.5	38	45	794	23.4	15.8	91.8	14.6	127	151	94	112	99	63	76	50	13	17.9	4.1	0.9
133 R	80	4.6	—	58	—	218	7.9	18.4	93.0	67.5	47	120	77	92	33	21	26	21	4	20.0	1.1	1.1
L	163	6.0	—	37	—	673	18.0	18.6	91.6	31.4	112	147	86	105	73	48	58	40	5	17.5	3.0	1.1
139 R	45	2.5	3.0	56	67	164	5.4	20.9	94.7	63.2	66	114	55	84	25	8	16	9	3	33.6	2.8	0.8
L	87	6.7	5.6	77	64	823	20.8	20.8	98.1	38.9	123	154	74	103	59	24	34	26	5	15.4	1.2	1.1
144 R	47	4.8	3.6	102	77	209	6.6	19.0	89.8	65.5	44	132	72	95	32	12	20	13	2	19.8	1.5	1.1
L	92	7.4	6.1	81	66	915	21.5	19.2	98.9	31.6	123	152	79	107	76	37	53	33	5	14.5	2.7	1.2
145 R	70		—	—	—	—	—	—	—	—	—	—	—	—	16	19	26	15	—	—	—	—
L	—		—	—		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 467

FAT LOADING TEST IN MALES WITH DIABETIC HEREDITY

AS COMPARED TO CONTROLS, DIABETICS AND CORONARY PATIENTS

BY

VEIKKO KALLIO

TURKU 1967

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University Hospital, Turku, Finland

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INTRODUCTION

During the last ten years increasing evidence has accumulated for the view that metabolic disturbances and even organic defects exist in the so-called prediabetic state in man. Because the most manifest sign in diabetes mellitus is hyperglycemia, efforts have been made to reveal abnormalities in carbohydrate metabolism pointing to the presence of a prediabetic state. It is now commonly accepted that for instance the glucose tolerance test gives valuable information about the risk of developing manifest diabetes mellitus.

However, we may well have overestimated the value of hyperglycemia as the primary feature of diabetes. The concept of a prevasculopathy inherited by potential diabetics has been presented. Although the insulin secretion may be sufficient to protect the prediabetic from developing hyperglycemia, it may not be normal enough to prevent the blood vessel walls from progressive damage. This could partly explain the clinical experience that severe atherosclerotic manifestations are often associated with mild or recently diagnosed diabetes mellitus.

It has been suggested that insulin might have an essential protective effect on the blood vessel wall. On the other hand, insulin plays an important role in the lipid metabolism and the lack of insulin results in hyperlipemia and hypercholesterolemia, which often characterize manifest diabetes mellitus. The atherosclerotic manifestations might then be attributable to these disturbances in lipid metabolism.

Some people with predisposition to diabetes mellitus exhibit high cholesterol, triglyceride or non esterified fatty acid values in blood. As the ability of the organism to metabolize fats is better reflected in the fat loading test, the present study was undertaken to determine whether any derangement of induced alimentary lipemia exists in close relatives of diabetic patients.

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However we may well have overestimated the value of hyperglycemia as the *primary feature* of diabetes. The concept of a prevasculopathy inherited by potential diabetics has been presented. Although the insulin secretion may be sufficient to protect the prediabetic from developing hyperglycemia it may not be normal enough to prevent the blood vessel walls from progressive damage. This could partly explain the clinical experience that severe atherosclerotic manifestations are *often associated* with mild or recently diagnosed diabetes mellitus.

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Some people with predisposition to diabetes mellitus exhibit high cholesterol triglyceride or non-esterified fatty acid values in blood. As the ability of the organism to metabolize fats is better reflected in the fat loading test the present study was undertaken to determine whether any derangement in induced alimentary lipemia exists in close relatives of diabetic patients.

PREVIOUS INVESTIGATIONS

Fat loading test in normal subjects

General aspects

Many factors play a part in the fate of the fat exogenously brought to the organism. When speaking of peroral fat loading tests the following factors should be taken into account: the type and amount of fat, the fasting lipid values, and the absorption and rate of entry of fat into the blood circulation through the lymphatics or (to a lesser degree) directly through the portal vein. The consequent clearing process, although far from being completely understood, seems to result from removal of chylomicrons by the peripheral tissues and the liver.

The fasting lipid values often give valuable information about a disturbance in lipid metabolism, and a fat tolerance test in such cases may add nothing to the information (ANGERVALL 1964). It cannot be denied, however, that a fat load may reveal disturbances during the clearing process and thus lead to more dynamic view on lipid metabolism.

In the following review, interest is directed chiefly to changes occurring during induced alimentary lipemia in chylomicronemia, serum turbidity, and various lipid fractions.

Chylomicronemia and serum turbidity

The chylomicrons are formed after absorption of dietary fat and consist mainly of long chain triglycerides with small amounts of cholesterol, phospholipids and protein as stabilizing carriers. They are responsible for the lactescence or turbidity of serum after a fatty meal. The counting of chylomicrons is performed on a microscopic slide (GAGE and FISH 1925). The method has later been used by FRAZER and STEWART (1936), and more recently by LEVY *et al* (1952) and CHAZAN *et al* (1964).

The counting of chylomicrons requires experience to give reliable results. Serum optical density (at 610—700 mμ) is, on the contrary, very easy to measure and is assumed to correlate well with the amount of neutral fat during the ascending part of the fat tolerance curve (BARRITT 1956, OSMON *et al* 1957, BROWN *et al* 1961, STUTMAN *et al* 1961, HOLLISTER 1963, ANGERVALL 1964). It has been suggested that a simple measurement of optical density is adequate for the clinical detection of aberrant responses to a fatty meal (OSMON *et al* 1957, HOLLISTER 1963).

Serum or plasma total lipids and total or esterified fatty acids

A fatty meal produces a consistent rise in the total lipids or serum fatty acids of normal adults. As stated earlier, many factors affect the degree and the duration of postprandial lipemia. Most important among these are the

rates of absorption and of removal of fat *from the blood* Individual variations are also great even after a standardized fat load

Man and Gildea (1932) studied the effect of the ingestion of large amounts (3 5—4 gm per kg of body weight) of fat on the serum fatty acids of 9 normal adults The average rise was 62 *per cent and the peak was reached in 4—6 hours*

The investigations of Hirsch and Carbonaro (1950) were performed on 21 normal adults using a fat load of 2—3 gm per kg of body weight The peak level of serum esterified fatty acids was reached in 3—4 hours and the rise varied between 24 and 146 per cent In the majority the rise ranged from 24 to 64 per cent of the fasting value

Pomeranze *et al* (1954) stated that physiologic postprandial lipemia reaches its peak within five hours and does not persist beyond eight hours Serum total fatty acids were estimated after a fat load of 204 gm

In the material of Barritt (1956) the 5 hour value of total lipids was already lower than the 3 hour value The fat content of the test meal was estimated at 60 gm

Osmon *et al* (1957) observed that the peak level of total lipids was reached in 3—4 hours after a fat load of 1 gm per kg of body weight

Brown *et al* (1961) estimated plasma total esterified fatty acids *after a fat* load of 0 5 litre of heavy *cream* In healthy medical students (age range 23—26 years) the mean 3-hour value was slightly higher than the mean 5 hour value After seven hours of fat load the mean value was lower than the fasting value The rise at three hours was 31 per cent of the fasting value

Stutman *et al* (1961) observed that the level of total fatty acids was 156 per cent of the fasting value three hours after the test meal consisting of 50—60 gm protein 200 gm carbohydrate and 1 5 gm of fat per kg of body weight At the end of six hours the values returned almost to the preprandial level

Serum or plasma triglycerides

In general the determinations of serum or plasma triglycerides *after* a fatty meal have revealed the same pattern as the determination of total lipids or total fatty acids This is to be expected because the test meals have predominantly consisted of neutral fat

By feeding 0 9—1 4 gm of fat per kg of body weight *Blix* (1926) found the maximal rise to occur 2—5 hours *after* the meal The average increase in neutral *fat* and in the p *fraction* (*petroleum ether fraction* containing neutral fat and *free cholesterol* but no phospholipids or cholesterol esters) was as low as 30 *mg* per cent

Havel (1957) estimated the triglycerides indirectly by subtracting lipid phosphorus and *cholesterol from the chloroform* methanol extract of blood serum The maximal change was seen four hours after a fat load of 1 5 gm cream fat per kg of body weight The rise of triglycerides was entirely due to *an increase in their concentration in very low density* (Sf 10) *lipoproteins*

Osmon *et al* (1957) also estimated the triglycerides indirectly concluding

that they are responsible for the rise in total lipids after a fatty meal

Direct estimation of serum triglycerides after a fatty meal was performed by NIKKILA and KONTTINEN (1962), BROWN *et al* (1963), DENBOROUGH (1963), HOLLISTER (1963), SHAH *et al* (1963) and ANGERVALL (1964) Using a fat load of 55 to 100 gm, the maximal increase was seen four hours after the fat ingestion, and the fasting level was usually reached again six to eight hours after the fat ingestion The rise was positively correlated to the fasting values (DENBOROUGH 1963, HOLLISTER 1963, ANGERVALL 1964) A significant increase in serum triglyceride values followed meals containing 30 gm, or more of fat (BROWN *et al* 1963)

Serum or plasma phospholipids

The increment of serum or plasma phospholipid concentration after a fatty meal is relatively small compared with that of triglycerides If large doses of fat (3—4 gm per kg of body weight) were ingested, a moderate rise followed (MAN and GILDEA 1932, POMERANZE *et al* 1954) *ANGERVALL (1964) observed* that a significant increase followed four hours after an even smaller amount (80 gm) of fat The rise occurred in phospholipids of very low density as well as in high density lipoprotein fractions (HAVEL 1957) After a fat load of 1—1 5 gm per kg of body weight, however, no significant changes followed (OSMON *et al* 1957 STUTMAN *et al* 1961), although in some cases a suggestive increase occurred during the latter half of the day (SHAH *et al* 1963)

Serum or plasma cholesterol

Although there is evidence indicating that cholesterol ingested in large doses may give rise to an increase in serum cholesterol values (BANG 1918, KNUDSON 1921, BURGER and HABS 1927), even contradictory results have been presented (SNAPPER and PARISEL 1933, BARREDA 1934) It is generally agreed that the changes in serum cholesterol after a test meal (1—5 gm of butter fat per kg of body weight) are inconsistent and cannot be used as indexes of fat absorption or their removal (OPPENHEIM and BRUGER 1943, HIRSCH and CARBONARO 1950, POMERANZE *et al* 1954, HAVEL 1957, HORLICK 1957, OSMON *et al* 1957, STUTMAN *et al* 1961, SHAH *et al* 1963, ANGERVALL 1964, BERKOWITZ 1965) NIKKILA and KONTTINEN (1962) and ANGERVALL (1964) even found a significant decrease in total serum cholesterol after the fat load in resting subjects — By contrast, HAMMERL *et al* (1962) demonstrated an increase of more than 22 per cent in the fasting cholesterol value after a fatty meal (1 gm per kg of body weight) in 71 per cent of men under 61 years of age Since the mean values are not given, their results are not comparable to those obtained by others

Serum or plasma non esterified fatty acids

The non esterified fatty acids (NEFA) constitute the blood lipid fraction primarily concerned with the supply of fats to tissues for oxidative metabolism (DOLE 1956, GORDON and CHERKES 1956 SPITZLER and MILLER 1956) The NEFA

values fluctuate rapidly and markedly in normal persons from time to time. It has been suggested that adipose tissue responds through some mechanism sensitive to the availability of non-fat calories liberating more or less NEFA into the blood and so maintaining a 'calorie homeostasis' (GORDON *et al.* 1957).

Certain factors are known to affect the level of circulating NEFA. The administration of glucose or insulin causes a sharp decrease in NEFA-concentration apparently by decreasing the release of fatty acids from tissue stores (DOLE 1956, GORDON and CHERKES 1956, GORDON *et al.* 1957, BIERMAN *et al.* 1957c, MUNKNER 1959a, HALES and RANDLE 1963, JAKOBSON *et al.* 1965). BIERMAN *et al.* (1957c) showed using C^{14} labeled palmitic acid that insulin did not accelerate the removal of NEFA from blood. In vitro studies by ENGEL and WHITE (1960) have shown that the action of insulin in retarding net NEFA release is mediated through a primary action on carbohydrate metabolism and not by direct inhibition of the lipolysis.

The effect of induced alimentary lipemia on NEFA has been studied both in laboratory animals (GROSSMAN *et al.* 1954, HAVEL and FREDRICKSON 1956) and in humans (GROSSMAN *et al.* 1955, ROBINSON *et al.* 1955, DOLE 1956, GORDON and CHERKES 1956, MUNKNER 1959a, NIKKILÄ and KONTTINEN 1962, SULLIVAN 1962, SHAH *et al.* 1963, HOLLISTER 1963, CASTELLA *et al.* 1966). There are individual variations apparently depending on the rate of absorption of fat, rate of transfer of triglyceride from blood, rate of hydrolysis of triglyceride, rate of utilization of NEFA and responsiveness of adipose tissue to the exogenous supply of fat. In general, however, there is a decrease, during the first two hours, in the mean concentration of NEFA which is followed by a clear rise with a peak 4 to 7 hours after the ingestion of fat.

When triglyceride was infused intravenously a clearcut increase of NEFA concentration occurred immediately (FORBES 1965). The distinct rise is obviously a result of the clearing process of chylomicron triglycerides which are transported through the plasma as NEFA. Evidence has been presented that the rise in NEFA concentration during the postabsorptive state is due to the heparin lipoprotein lipase mechanism (GROSSMAN *et al.* 1954, 1955, SPITZER and MILLER 1956, ENGELBERG 1960, BARBORIAK *et al.* 1965). The work done on lipoprotein lipases has recently been summarized by WILLS (1965).

Some other mechanisms, however, certainly play an additional role in the clearing process. It has been argued that the liver is one major site of lipolysis (FREDRICKSON and GORDON 1958, OLIVECRONA *et al.* 1961, DOLE and HAMLIN 1962). The liver should thus be responsible for the rise in non-esterified fatty acid concentration after a fatty meal.

Influence of age and weight on fat loading test

Age. The effect of age on chylomicron counts was studied by BECKER *et al.* (1960). They observed after a fat load of 0.5 gm of oleomargarine per kg of body weight that at the end of a 5 hour

that they are responsible for the rise in total lipids after a fatty meal.

Direct estimation of serum triglycerides after a fatty meal was performed by NIKKILA and KONTTINEN (1962), BROWN et al. (1963), DENBOROUGH (1963), HOLLISTER (1963), SHAH et al. (1963) and ANGERVALL (1964). Using a fat load of 55 to 100 gm the maximal increase was seen four hours after the fat ingestion and the fasting level was usually reached again six to eight hours after the fat ingestion. The rise was positively correlated to the fasting values (DENBOROUGH 1963, HOLLISTER 1963, ANGERVALL 1964). A significant increase in serum triglyceride values followed meals containing 30 gm or more of fat (BROWN et al. 1963).

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The non esterified fatty acids (NEFA) constitute the blood lipid fraction primarily concerned with the supply of fats to tissues for oxidative metabolism (DOLL 1956, GORDON and CHERKES 1956, SPITZLER and MILLER 1956). The NEFA

values fluctuate rapidly and markedly in normal persons from time to time It has been suggested that adipose tissue responds through some mechanism sensitive to the availability of non fat calories liberating more or less NEFA into the blood and so maintaining a caloric homeostasis (GORDON *et al* 1957)

Certain factors are known to affect the level of circulating NEFA The administration of glucose or insulin causes a sharp decrease in NEFA-concentration apparently by decreasing the release of fatty acids from tissue stores (DOLE 1956 GORDON and CHERKES 1956 GORDON *et al* 1957 BIERMAN *et al* 1957 c, MUNKNER 1959 a HALES and RANDLE 1963 JAKOBSON *et al* 1965) BIERMAN *et al* (1957 c) showed using C^{14} labeled palmitic acid that insulin did not accelarate the removal of NEFA from blood In vitro studies by ENGEL and WHITE (1960) have shown that the action of insulin in retarding net NEFA release is mediated through a primary action on carbohydrate metabolism and not by direct inhibition of the lipolysis

The effect of induced alimentary lipemia on NEFA has been studied both in laboratory animals (GROSSMAN *et al* 1954 HAVEL and FREDRICKSON 1956) and in humans (GROSSMAN *et al* 1955 ROBINSON *et al* 1955 DOLE 1956 GORDON and CHERKES 1956 MUNKNER 1959 a NIKKILA and KONTTINEN 1962 SULLIVAN 1962 SHAH *et al* 1963 HOLLISTER 1963 CASTELLI *et al* 1966) There are individual variations apparently depending on the rate of absorption of fat rate of transfer of triglyceride from blood rate of hydrolysis of triglyceride rate of utilization of NEFA, and responsiveness of adipose tissue to the exogenous supply of fat In general, however, there is a decrease during the first two hours in the mean concentration of NEFA which is followed by a clear rise with a peak 4 to 7 hours after the ingestion of fat

When triglyceride was infused intravenously a clearcut increase of NEFA concentration occurred immediately (FORBES 1965) The distinct rise is obviously a result of the clearing process of chylomicron triglycerides which are transported through the plasma as NEFA Evidence has been presented that the rise in NEFA concentration during the postabsorptive state is due to the heparin lipoprotein lipase mechanism (GROSSMAN *et al* 1954 1955, SPITZER and MILLER 1956 ENGELBERG 1960 BARBORIAK *et al* 1965) The work done on lipoprotein lipases has recently been summarized by WILLS (1965)

Some other mechanisms however certainly play an additional role in the clearing process. It has been argued that the liver is one major site of lipolysis (FREDRICKSON and GORDON 1958 OLIVECRONA *et al* 1961 DOLE and HAMLIN 1962) The liver should thus be responsible for the rise in non esterified fatty acid concentration after a fatty meal

Influence of age and weight on fat loading test

Age The effect of age on chylomicron counts was studied by BECKER *et al* (1950) They observed after a fat load of 0 5 gm of oleomargarine *per kg of* body weight that at the end of a 5 hour

period, the values for young subjects (mean age 18.2 years) had returned to fasting levels. The counts for the old patients (mean age 75.6 years), on the other hand, were still rising after five hours. The peak of the curve for old subjects was reached between 8 and 12 hours, as contrasted with the peak at 2½ to 3 hours for young patients. By adding pancreatic lipase to the test meal of the aged individuals the authors showed that the peak was attained much sooner and the total number of chylomicrons was markedly lower. They thus concluded that in aged subjects there is distinct decrease in the rate of fat absorption.

Age did not significantly affect the postprandial serum turbidity values in the material of SCHWARTZ *et al.* (1952), although the values were slightly higher in the older group (over 40 years of age) than in the younger group (40 years or less).

HERZSTEIN *et al.* (1953) determined the total lipids after a fat meal of 1 gm per kg of body weight. The peak level of lipemia was reached later in the aged (mean age 62 years) than in the young group (mean age 24.9 years). No significant differences were found in the degree or disappearance rate of lipemia.

BROWN *et al.* (1961) found that, as regards plasma turbidity, total esterified fatty acids and lipid I^{131} levels, young students (23 to 26 years of age) did not differ from healthy men (mean age 51.3 years) except that in the latter group the plasma optical density reading and the total esterified fatty acid level were significantly higher seven hours after fat feeding.

BARRIT (1956) was not able to demonstrate any significant correlation between age and postprandial lipemia. Contrary to the above investigators, he stated that any tendency relating to age seemed to show an increased lipemia in younger people. Neither BOUCHIER and BRONTE STEWART (1961), by determining the optical density, nor ANGERVALL (1964), by determining the glyceride glycerol level after a fat load, could show any difference between young and old age groups.

Results pointing to increased postprandial lipemia in younger age groups have been reported by GRUNER and HILDEN (1953) and HAMMERL *et al.* (1962). The former investigators observed a higher chylomicron count and the latter a greater percentage of significant increase in serum cholesterol.

Weight. Moderately obese persons seem to have fat tolerance curves similar to those of persons with normal weight (OPPENHEIM and BRUGER 1943, BARRIT 1956, ANGERVALL 1964). POMERANZE *et al.* (1954) noted, however, that in extremely obese subjects (weight more than 250 lbs), the peak level of postprandial lipemia is reached three hours later than in normal subjects.

Fat loading test in clinical use

MORETON (1950) has presented a theory according to which the development of atherosclerosis in otherwise normal human beings may be the direct result of recurrent alimentary chylomicronemia due to repeated ingestion of fatty meals over a lifetime; prolonged postprandial lipemia is considered

the atherogenic factor This theory was based on the finding that atherosclerotic subjects present higher and longer lasting chylomicron counts after a fatty meal (MORETON 1947)

Since then many investigations on fat tolerance have been performed in subjects with atherosclerotic manifestations especially in survivors of myocardial infarction A more intense and more long continued lipemia after an oral fat load has been found in a great majority of these patients as compared to healthy age matched control subjects (SCHWARTZ *et al* 1952 POMERANZE *et al* 1954 BARRIT 1956 BOUCHIER and BRONTE STEWART 1961 BROWN *et al* 1961 STUTMAN *et al* 1961) Similar results have been obtained when the disappearance rate of ingested I^{131} labeled fat has been used as an index of lipemic response (IBKOFF *et al* 1958 SELLER *et al* 1959 BERKOWITZ 1960 BROWN *et al* 1961 LEVINE and COHEN 1962 MALAMOS *et al* 1962 BERKOWITZ 1965)

The nine hour postprandial serum optical density was found to be a useful and effective tool in separating the healthy and coronary group (STUTMAN *et al* 1961) This value was clearly higher in coronary patients than in healthy subjects A considerable overlap of individual nine hour optical density values was reported by BROWN *et al* (1961) In their investigation the nine hour values for total esterified fatty acids allowed a better separation between these groups At nine hours after the fatty meal only 2 patients with ischemic heart disease (7 per cent of the group) had total esterified fatty acid levels below the fasting level whereas 83 per cent of the healthy group fell in this category

Using vitamin A and E loading tests, PELKONEN (1963) found a significantly higher mean increase from the basal level in the coronary group than in the healthy group Vitamin A and tocopherol being lipids of purely exogenous origin in the organism it was concluded that the marked increase in their concentration was due to impaired disappearance rate

Blood lipids in diabetes mellitus

Fasting lipid values

Several investigators agree that many patients with diabetes mellitus at least of recent onset show abnormally high levels of circulating lipids (BLOOR *et al* 1916 JOSLIN *et al* 1917 BLAU and NICHOLSON 1920 WISHART 1922 ARNOLDI and COLLAZO 1924 BLIX 1926 MAN and PETERS 1935 KATCH and KRAINICI 1939 KALAJA and HELVE 1947, HIRSCH and CARBONARO 1950 BARACH and LOWY 1952 DINE and JACKSON 1952 DINE *et al* 1953 WAAGSTEIN 1955 ADLERSBERG and EISLER 1959 HAMWI *et al* 1962 SULLIVAN *et al* 1962 BRUNNER *et al* 1964) It has been reported that especially in diabetic acidosis the serum cholesterol and phospholipid levels and β lipoprotein fractions are higher than after treatment for acidosis (MAN and PETERS 1934 KATCH and KRAINICK 1939 HARRIS *et al* 1953 TULLER *et al* 1954 WOLFF and SALT 1958) On the other hand no uniform relation of lipemia to acidosis has been observed by BLOOR *et al* (1916) ALLEN (1917) BANG (1919) and CHAIKOFF *et al* (1936)

Efforts have been made to correlate hyperglycemia and hyperlipemia in diabetics. BLAU and NICHOLSON (1920) found, in their material of 24 diabetics, that the changes in blood fat parallel those of blood sugar, but only in a minority of patients. HIRSCH *et al* (1953), and WAGSTEIN (1955) showed that the blood lipids, especially triglycerides, and glucose levels change parallelly. WOLFF and SALT (1958) stated that the mean levels of β lipoproteins, cholesterol and esterified fatty acids were significantly higher in diabetic children with blood sugar levels above 200 mg per cent than in those under 200 mg per cent. BANG (1919) found no uniform relation of cholesterol and phosphatid levels to blood glucose, nor could TRAISMAN *et al* (1960) show any correlation between glucose levels and cholesterol or β lipoprotein levels.

Diabetic complications, especially diabetic glomerulosclerosis, may be associated with hyperlipemia. LANGELBERG *et al* (1952) reported high values of Sf 12—20 of Sf 20—35, and also of serum cholesterol and phospholipids in 17 diabetics with glomerulosclerosis. They pointed out that the rise in Sf 12—20 may be an early sign of this complication. KEIDING *et al* (1952) also observed high lipid values in patients with diabetic nephropathy.

BARACH and LOWY (1952) found that the hyperlipemia was most marked in patients with arterial calcification and enlargement of the heart. In the material of ADLERSBERG and EISLER (1959) the serum triglycerides were high in diabetics with vascular complications, especially when the fasting blood sugar content was more than 150 mg per cent. The levels of serum cholesterol and phospholipids were only moderately increased or unchanged. A moderate, but significant rise in phospholipids was recorded by VITELLI *et al* (1965).

MAY and PETERS (1935) were unable to demonstrate any correlation between serum cholesterol and the degree of atherosclerotic manifestations or the severity of diabetes itself. The same conclusion was made by KEMPE *et al* (1952), who determined Sf 11—20 and serum cholesterol in diabetic children.

PETERSEN (1953) found no correlation to exist between the severity of diabetic retinopathy and serum cholesterol or phospholipids. He suggested that the diabetic vasculopathy and atherosclerosis are due to entirely different metabolic aberrations.

The concentration of non esterified fatty acids is high not only in diabetic ketoacidosis (LAURELL 1956) but in the diabetic state in general (BIERMAN *et al* 1957 a, MUNKNER 1959), SULLIVAN *et al* 1962). This might reflect the lack of α glycerophosphate in the adipose tissue due to impaired glucose utilization (JEANRENAUD 1961). In the absence of α glycerophosphate the esterification of non esterified fatty acids is blocked in the adipose tissue, which results in increase of circulating non esterified fatty acids. HALES and RANDLE (1963) suggest that diabetics may show antagonism not only to the hypoglycemic action of insulin but also to the important action of insulin in suppressing release of non esterified fatty acids from adipose tissue. — When diabetic patients were treated with sulphonylurea preparations

the concentration of serum non esteri fied fatty acids decreased (BIERMAN et al 1957b OWEN 1962) probably as a result of enhancement of lipogenesis in adipose tissue mediated by the release of endogenous insulin and increased glucose uptake by these tissues

Fat loading test

ALLEN stated, as early as 1917 that alimentary lipemia in diabetics is higher and of longer duration than in normals ARNOLDI and COLLAZO (1924) presented data on one diabetic whose plasma was still lipemic 8 hours after the fat load The problem of diabetic alimentary lipemia was more extensively studied by BLIX (1926) who performed fat loading tests in both mild and severe cases of diabetes The rise of the blood fat curve after fat ingestion (fat intake 1 0—2 6 gm per kg body weight) in most in stances did not exceed the rises observed in normal individuals on a diabetic diet In some cases it did not even exceed those observed in normals on ordinary diet Nor did the alimentary lipemia as a rule last longer in diabetics than in normals No association was found be tween the mobility of the blood fat curve after fat ingestion and the temporary height of the blood fat level

HIRSCH and CARBONARO (1950) deter mined serum esterified fatty acids in 21 diabetics after a fat load of 2—3 gm per kg body weight They found that the peak of lipemia was delayed and the degree of lipemia more marked than in normals. In severe diabetes the lipemia was higher although the percentile rise was about the same as in mild diabe tes — In a later study HIRSCH et al (1953) found that the alimentary lip emia was related to blood sugar values

LEVY et al (1952) studied chylomicro graphs and nephelographs of 13 aged diabetics and found distinct differences as compared with 13 aged non-diabetic and 12 young subjects. They suggest that in diabetics either the absorption or the disposition of fat or both, may differ from normal

By feeding I[131] labeled triolein to 27 persons with diabetes mellitus SANDBERG et al (1960) demonstrated abnormal curves especially in diabetics under 60 years of age with demonstrable evidence of atherosclerotic complications Lesser degrees of abnormality were found in diabetics under 60 years of age with no evidence of atherosclerotic complications The curves were almost identical with a previously reported myocardial in farction group

WADDEL and GEYER (1957) studied the problem using depancreatized dogs which were given fat emulsion intra venously They noted that animals main tained on insulin can clear fat from the blood normally whereas deprivation of insulin results in delayed clearance of all lipid components — On the other hand BALODIMOS et al (1962) could not show any differences in the clearance of intravenously administered triolein I[131] between diabetic and normal subjects They concluded that this might impli cate the gastrointestinal tract as the main basis of the differences observed between diabetics and normal subjects when oral administration of fat is em ployed Intravenously administered fat however may be cleared by some mecha

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nism other than the orally fed fat. It is probable that intravenously injected emulsion particles are removed for the most part by the reticuloendothelial system, which thus does not seem to be damaged in diabetic subjects.

The prediabetic state and subclinical diabetes mellitus

General aspects

Much confusion has existed regarding the definition of the prediabetic state in man. Practically all investigators agree that a prediabetic state exists in a person with identified diabetic parents. While it was earlier considered that the prediabetic state is characterized for example by a positive response to cortisone glucose tolerance test (FAJANS and CONN 1954, 1959, 1961, JACKSON 1954, 1960, 1961, JACKSON and WOOLF 1957, GOTO *et al.* 1960, WEST 1960), it has lately been stressed that even an abnormal cortisone glucose tolerance test points to the presence of subclinical or chemical diabetes (CONN and FAJANS 1962, CAMERINI-DAVALOS *et al.* 1963, STEINKE *et al.* 1963). According to CAMERINI DAVALOS (1965), prediabetes can be defined as "the condition of those persons who will eventually develop diabetes but in whom no abnormalities of carbohydrate metabolism are demonstrable."

In addition to close relatives of diabetics, there are individuals who can be regarded as prediabetics according to the above definition of CAMERINI DAVALOS, e.g. women who have borne overweight children or present certain obstetrical abnormalities. In both of these groups, the following abnormal findings have been observed:

- elevated insulin-like activity (ILA) of blood serum in the fasting state (STEINKE *et al.* 1961, DITSCHUNEIT *et al.* 1963, STEINKE *et al.* 1963),
- increased antagonism to insulin in the plasma albumin fraction called synalbumin (VALLANCE OWEN and LILLEY 1961, VALLANCE OWEN and ASHTON 1963),
- hyperresponsiveness of growth hormone secretion following glucose administration (UNGER 1965), and
- increased secretion of adrenocorticotropic hormone and reversed diurnal rhythm with a peak level of ACTH at midnight (PFEIFFER 1965).

The abnormalities in microcirculation as well as those of lipid metabolism will be discussed more extensively in the following section. As the sensitized oral glucose tolerance test is an important tool in the detection of subclinical diabetes mellitus, a review of its value is also presented.

Small blood vessel changes

Characteristic changes in biopsy material from the ear lobe and gingiva studied by electron microscope have been found in prediabetics (CAMERINI DAVALOS *et al.* 1963, CAMERINI DAVALOS 1965). The dermal capillaries were frequently constricted compared with normal. The venules showed some degree of endothelial cell separation as well as expansion of the potential space between the basement membrane and the endothelial cell. Thirdly, the dermal elastic

tissue usually appeared fibrillar and much more dense in prediabetics than in normals

The bulbar conjunctivae offer a good opportunity to study the condition of the small blood vessels and possible morphological changes in them. DITZEL *et al* (1954, 1957) examined children of young diabetic mothers under a stereoscopic dissecting microscope. They found an increased (more than 1 3) arteriole-venule (a/v) ratio in 43 per cent of 100 children examined in 1953 and in 35 per cent of the same children examined in 1956. They suggest that this increase of a/v ratio is due to the excessive vasomotor response which characterizes the prediabetic state and results in *arteriolar constriction* and venular distension. The children who exhibited the abnormal vascular responses were predominantly those with hyperglycemic tolerance tests. They were thus no longer 'prediabetics' but 'subclinical diabetics' according to the definition of CAMERINI DAVALOS.

CAMERINI DÁVALOS *et al* (1963) measured the ratio of width of venules to that of arterioles in photographs of the bulbar conjunctiva. The mean of the venule-arteriole ratio in 20 normal subjects was 2.29 ± 0.26 as compared to *4.22 ± 0.5* in *25 genetically* predisposed prediabetics with normal glucose tolerance tests. Twenty three out of 25 (92 per *cent*) *showed values above 2.81 (mean* for normals + 2 S D). As regards the retinal vasculature there were no significant differences between the prediabetic and control subjects.

CHAZAN *et al* (1964) examined 80 apparently healthy women who had borne at least *one* baby weighing more than 4 kg. The bulbar conjunctivae were examined by a Zeiss slitlamp at a magni*fication of ×25. Micropools* were classified as follows: Type I venular and on one side of the vessel, Type II venular *and fusiform or saccular extending from* both sides of the vessel, and Type III capillary. Red cell aggregation (sludge) *was recorded when present in arterioles* in both the temporal and nasal aspects of the conjunctiva of both eyes. Micro*pools were found as often in those with* normal glucose tolerance test ('prediabetics', 65 per cent) as in those with *diabetic (73 per cent) or borderline* (69 per cent) glucose tolerance test ('subclinical diabetes'). At all ages the venular and fusiform or saccular micropool (Type II) was most common. Arteriolar sludge was found to be more common in subjects with a diabetic glucose tolerance test; in this group it was seen in 52 per cent as compared to 35 per cent in subjects with a *normal* glucose tolerance test.

WOLFSOHN and LAVIEL (1964) reported that conjunctival *microaneurysms* were discovered in about 7 per cent of 2000 non-diabetics attending the eye clinic. 126 *patients with microaneurysms* were further investigated by means of cortisone glucose tolerance test. 37 subjects or 29 per cent were found *to have* a positive cortisone glucose tolerance test ('subclinical diabetes'), 35 subjects or *28 per cent*, had a borderline cortisone glucose tolerance test and the rest, 54 were 'as yet non-diabetic although possibly prediabetic'. The authors suggest that deep microaneurysms, especially at the *peripheral* part of the conjunctiva,

are very probably associated with diabetes, and can be used as a tool in the early detection of diabetes

Blood lipids

ALBRINK *et al* (1962) presented a material consisting of apparently healthy male factory employees A family history positive for coronary disease or diabetes mellitus was associated with higher fasting triglyceride and cholesterol values than those found in the group with a negative family history No data are given about the glucose tolerance in these subjects, hence it is not possible to decide whether they represent "prediabetic" or "subclinical diabetic" subjects

CHAZAN *et al* (1964) performed chylomicron counts in presumably healthy mothers who had borne at least one baby exceeding 4 kg in weight Hyperchylomicronemia was found in 52 per cent of the mothers with a positive glucose tolerance test The subjects with a normal glucose tolerance included 28 per cent with hyperchylomicronemia Hypercholesterolemia did not parallel hyperchylomicronemia and values exceeding 260 mg per 100 ml were found in only 8 out of 40 subjects with positive or borderline glucose tolerance test In subjects with a normal glucose tolerance test only 2 out of 40 presented high cholesterol values

Direct estimations of serum triglycerides were performed by JAKOBSON *et al* (1965) in 60 close relatives of known diabetics The mean values of serum triglycerides and cholesterol were somewhat although not significantly higher in the subjects with a positive response to prednisone glucose tolerance test (subclinical diabetes) than in the subjects who showed less impairment of glucose tolerance The findings in the latter group accord with those presented by CAMERINI DAVALOS and co-workers (CAMERINI DAVALOS 1965) who did not find any difference between normal and "prediabetic" subjects in the levels of serum cholesterol and triglycerides in the fasting state

A tendency towards increased levels of circulating non esterified fatty acids in the fasting state has been observed in "prediabetics" as compared with the normal group (CATELLIER *et al* 1964 JAKOBSON *et al* 1965, PFEIFFER 1965) After an intravenous glucose tolerance test (CATELLIER *et al* 1964) or prednisone sensitized oral glucose tolerance test (JAKOBSON *et al* 1965), a drop of NEFA concentration was observed both in normal subjects and in close relatives of diabetics However, the decrease was more pronounced and delayed in the group of "prediabetics" and especially in the group of "subclinical diabetics" than in normal subjects While, according to CATELLIER *et al* (1964) this may be one of the first non glucose abnormalities in subjects genetically predisposed to diabetes JAKOBSON *et al* (1965) think that this is attributable to a delayed insulin action caused by the increased release of fatty acids for oxidation and consequent inhibition of glucose uptake in the tissues In diabetics examined by HALES and RANDLE (1963) the above mechanism was thought to be responsible for the delayed rate of fall of non esterified fatty acid concentration after an oral glucose load

Sensitized glucose tolerance tests

CONN *et al.* (1948) observed that temporary diabetes mellitus could be induced in man by administration of adrenocorticotrophic hormone. BERGER (1952) was the first to use it in order to increase the sensitivity of glucose tolerance test. In 14 siblings of diabetics 100 mg of adrenocorticotrophin administered one hour before the glucose tolerance test resulted in higher blood sugar values than those observed after an ordinary glucose tolerance test. Among 18 normal subjects over 50 years of age only one showed a positive test. BERGER's criteria for a positive corticotrophin sensitized glucose tolerance test were: blood sugar level higher than the fasting level three hours after glucose loading and/or higher blood sugar values during the corticotrophin glucose tolerance test.

The method has later been standardized and used especially by FAJANS and CONN (1954, 1959, 1961). They have used cortisone acetate in amounts of 50 mg (in subjects less than 160 lbs* of weight) and 62.5 mg (in subjects over 160 lbs of weight) given 8½ hours and again two hours before the glucose tolerance test. In their material published in 1954 consisting of 75 subjects with a family history of diabetes and normal glucose tolerance test they found positive cortisone glucose tolerance tests in 18 subjects (or 24 per cent). In 37 normal subjects there was only one positive response. — Criteria of a positive cortisone glucose tolerance test were values over 160 mg per cent one hour and 140 mg per cent/two hours of true glucose determined in venous blood. — It has been questioned whether a positive response in the cortisone glucose tolerance test has any predictive value in regard to a future diabetes. The follow up studies by FAJANS and CONN (1959) have shown that 25 per cent of altogether 40 subjects with a positive response to the initial cortisone glucose tolerance test had developed diabetes and another 10 per cent had developed probable diabetes.

The results of FAJANS and CONN have subsequently been confirmed for instance by GOTO *et al.* (1960) and SANDERS (1961). The former investigators found that a normal group of 10 subjects revealed little or no change in the glucose tolerance curve after pretreatment with 10 mg of prednisolone two hours before the test. In a group of 17 healthy persons with a family history of diabetes mellitus six subjects (35 per cent) showed a diabetic curve and the test was normal in only three. Their criterion for a positive prednisolone glucose tolerance test was a peak of more than 200 mg per cent of glucose estimated from capillary blood according to a modified Hagedorn-Jensen method.

SANDERS (1961) found that among 42 diabetic relatives there were 25 or 58 per cent of positive reactors to prednisolone (1 mg/14 lbs* body weight 12 hours and again two hours before the glucose tolerance test). A difference of more than 20 mg per 100 ml between the pre- and postprednisolone blood glucose values at any two of the three points

* 160 lbs = [illegible] kg

* 14 lbs = 6.35 kg

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OBJECTS OF THE PRESENT STUDY

The study was carried out keeping in view the following main objects

1 to determine the nature of the fasting serum lipid values in close relatives of diabetics as compared to those of control subjects recently diagnosed diabetics and coronary patients,

2 to determine whether the postalimentary lipemia of close relatives of diabetics is normal or in any respect similar to that found in diabetics and coronary patients

3 to study close relatives of diabetics with a view to discovering the correlation if any, between their fasting serum lipid values or values after fat loading and their glucose tolerance, conjunctival vascular changes or body weight,

4 to discover the possible advantage of the fat loading test over the determination of fasting serum lipid values, and the lipid fraction to be preferred

one, one and a half, and two hours, was taken to indicate a positive result The significant changes in the prednisolone glucose tolerance test occurred during the second hour — This method does not seem to be of value in examining subjects over 40 years of age, since a positive response was almost as common in the control group as in the diabetic relatives over this age

JAKOBSON *et al* (1956) perfomed prednisone glucose tolerance tests in 60 close relatives (parents, children or siblings) of diabetics The test was performed according to the original cortisone glucose tolerance test described by FAJANS and CONN (1954), substituting 10 mg of prednisone for each 50 mg of cortisone 13 subjects (21 7 per cent) showed a positive response, i e values over 160 mg per cent/one hour and 140 mg per cent/two hours of true" glucose determined in venous blood

GUNN *et al* (1965) stated that the majority of subjects with a history of diabetes in father, mother or sibling will show a positive response to the prednisone glucose tolerance test by 45 years of age The test was performed by administering a single oral dose of 30 mg of prednisone eight hours before starting the glucose tolerance test The test was judged abnormal if either the thirty minute or one hour blood sugar exceeded 159 mg per 100 ml and the two hour value exceeded 139 mg per 100 ml

WEST (1960) has arrived at less promising results as regards the value of the cortisone glucose tolerance test Such tests were performed in 26 persons with normal glucose tolerance, whose parents were both diabetics Their responses to cortisone were not significantly different from those of a control group with normal glucose tolerance and no family history of diabetes In evaluating WEST's results it must be borne in mind that he determined only the fasting and two hour blood glucose level, which may lead to erroneous conclusions

The cortisone glucose tolerance test has also been criticized by JACKSON (1961), who points out that many false negative results may be obtained He found that a number of definite mild diabetics and others who are almost certainly prediabetics show no worsening of glucose tolerance after cortisone In his opinion this test is difficult to interpret and cannot be recommended for routine use

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4 to discover the possible advantage of the fat loading test over the determination of fasting serum lipid values and the lipid fraction to be preferred

MATERIAL

The material comprised altogether 82 subjects, consisting of controls, males with diabetic heredity, diabetics, and coronary patients. The age distribution and mean age of the different groups is presented in Table 1.

Control subjects

This group comprised 22 males in the age range of 15 to 48 years (mean age 27.1 years). Mean weight in this group was 68 kg ranging from 52 to 96 kg, and mean height 174 cm with a range from 162 to 191 cm. These patients were examined in hospital because of acquired valvular or congenital heart disease. They presented neither signs of cardiac decompensation nor any evidence of disturbed lipid metabolism nor diabetic heredity. Their dietary habits, as judged by their own statements, were of the usual Finnish type (30—40 per cent of total calories derived from fats).

Males with diabetic heredity

This group consisted of 22 males between the ages of 16 and 42 years (mean 27.7 years). Their mean weight was 78 kg ranging from 59 to 106 kg and mean height 177 cm with a range from 164 to 191 cm. The criterion for admission to this group was that one of the parents had diabetes mellitus. In addition, eight subjects had other relatives with diabetes mellitus.

The subjects were hospitalized during the examination. Endogenous creatinine clearance values were normal in all except one in whom it was 57 ml/per min. An abnormal ECG with inverted T waves in precordial leads was observed in another subject but he had no history of anginal pain.

The standard oral glucose tolerance test was normal in all the subjects. Two persons showed a borderline curve and three others presented glucosuria during the glucose tolerance test with normal blood glucose levels.

The cortisone glucose tolerance test was performed according to the original method described by Fajans and Conn (1954). Two subjects showed a positive response to this test, and both also glucosuria during the test. A borderline response was obtained in two subjects and three others showed glucosuria with normal blood glucose levels. Blood glucose determinations were performed from capillary blood according to the method of Hyvärinen and Nikkilä (1962).

Examination of the bulbar conjunctivae* revealed the following changes

* The examination of the bulbar conjunctivae was carried out as a team work under the direction of Professor A. Oksala, M.D.; the preliminary results have been presented at the annual meeting of the Scandinavian Society for the Study of Diabetes in 1965 (Oksala et al. 1966) and will be published in detail elsewhere.

Table 1 Age distribution of control subjects, males with diabetic heredity, diabetics and coronary patients

	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	Mean age years
Control subjects	6	4	[illegible]	1	4		1	—		—	27 1
Males with diabetic heredity	[illegible]		[illegible]		5	1	—		—		27 7
Diabetics		[illegible]	1	[illegible]	2	2	2	[illegible]	—	—	37 9
Coronary patients	—		—		1	1	3	10	7	3	52 8

Marked intravascular erythrocyte aggregation was seen in eight subjects (38 per cent) An increased arteriole venule ratio (>1 3) was the most common finding being present in 16 subjects (76 per cent) Clearly increased tortuosity of the small blood vessels was found in 10 subjects (48 per cent), one to three capillary aneurysms in five subjects (24 per cent), and venular saccular micropools in a total of 14 subjects (67 per cent), seven of whom showed four or more micropools Only six out of 21 subjects showed no demonstrable changes or only minor abnormalities

Patients with diabetes mellitus

This series comprised 13 males aged from 21 to 53 years (mean 37 9 years) The patients were untreated and had had symptoms for 1 to 6 months before admittance to hospital No case with severe acidosis is included and slight acidosis was observed in only two patients — The patients were not blood relations of the subjects included in the group males with diabetic heredity

The diabetics showed no evidence of advanced atherosclerotic changes The peripheral pulsations and 12 lead ECG were normal No history of chest pain was obtained

Coronary patients

This group consisted of 25 male patients with verified myocardial infarction or angina pectoris with ECG-changes subsequently treated in the University

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	15—19	20—24	25—29	30—34	35—39	40—44	45—49	50—54	55—59	60—64	Mean age years
Control subjects	8	4	[illegible]	1	4	[illegible]	1	—	[illegible]	—	27.1
Males with diabetic heredity	[illegible]	1	[illegible]	[illegible]	[illegible]	3	—		—		27.7
Diabetics			1	[illegible]	2	[illegible]	[illegible]	[illegible]	—	—	37.9
Coronary patients	—		—	—	1	1	3	10	7	[illegible]	[illegible]

Marked intravascular erythrocyte aggregation was seen in eight subjects (38 per cent). An increased arteriole venule ratio (>1 3) was the most common finding, being present in 16 subjects (76 per cent). Clearly increased tortuosity of the small blood vessels was found in 10 subjects (48 per cent), one to three capillary aneurysms in five subjects (24 per cent), and venular saccular micropools in a total of 14 subjects (67 per cent), seven of whom showed four or more micropools. Only six out of 21 subjects showed no demonstrable changes or only minor abnormalities.

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Fat loading test

After an overnight fast, beginning at 7.00 p.m. the first blood sample was drawn at 7.00 a.m. and 200 ml of cream* containing 30—32 per cent of fat was then administered. Blood samples were drawn 2, 4, 6, 8 and 10 hours after the ingestion of cream. The samples were centrifuged immediately and blood serum stored at +4°C. The samples were analysed within 2—3 days after the withdrawal.

During the fat loading test the persons were kept in bed and were allowed water but no food or tobacco.

Determination of serum lipids

General principles

Serum optical density was measured at 620 mμ against water blank with Beckman B spectrophotometer (BROWN *et al.* 1961).

Total lipids were determined from duplicate samples of 1 cc blood serum using the chloroform-methanol extraction and purification method described by SPERRY (1955).

Non-esterified fatty acids (NEFA) of total lipids were methylated with diazomethane, the resulting methyl esters were then isolated through sublimation. The microsublimation method of STOFFEL *et al.* (1959) was modified as described later. Quantitative determination was carried out using the hydroxamate reaction (STERN and SHAPIRO 1953, CARLSON and WADSTRÖM 1958).

Triglycerides, free cholesterol and cholesterol esters were fractionated using silicic acid column chromatography (CREECH 1961). Two fractions were eluted: 1) sterol esters and 2) free cholesterol, triglycerides and diglycerides. From these eluates cholesterol was determined with the p-toluenesulphonic acid reaction (PEARSON *et al.* 1953) and the di- and triglycerides were determined using the hydroxamate reaction, as were the methyl esters of NEFA.

Phospholipids were estimated from the serum separately using the method of FISKE and SUBBAROW (1925) as described by KING and WOOTTON (1959).

Technique of determination

NEFA: 1 ml ethyl ether and 1 cc of freshly distilled diazomethane is pipetted into each of the bottles containing the duplicate samples of total lipids. The reaction mixtures are allowed to stand fifteen minutes at room temperature and are then transferred into sublimation tubes. The samples are evaporated to dryness in a nitrogen stream and placed in a +70 C heating block. The tubes are sealed with cold finger condensators and kept in vacuum for 45 minutes. The cold fingers are then detached cautiously and the sublimed methyl esters are washed off in 3 ml of Bloor's solvent. Two

* Standard Heavy cream Valio

Hospital of Turku Mean age was 52.8 years ranging from 36 to 64 years No patients with manifest diabetes mellitus were included The patients were not, however, subjected to glucose tolerance tests, so this group may include several patients with slightly impaired glucose tolerance

Fat loading test

After an overnight fast beginning at 7 00 p m the first blood sample was drawn at 7 00 a m and 200 ml of cream* containing 30—32 per cent of fat was then administered Blood samples were drawn 2 4, 6 8 and 10 hours after the ingestion of cream The samples were centrifuged immediately and blood serum stored at +4°C The samples were analysed within 2—3 days after the withdrawal

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* Standard [illegible] cream Valio

methyl oleate standards of 1 µEq per 3 ml each and one method blank of 3 ml Bloor's solvent are added to the series 1 ml of alkaline hydroxyl amine reagent is added, the tubes are sealed and allowed to stand 30 minutes in water bath (35—37° centigrade) Thereafter the tubes are cooled by running water and 0 5 ml of 3 n HCl is added After mixing, 0 5 ml of $FeCl_3$ reagent is added, the tubes are shaken and after 30 minutes the samples are measured at 520 mµ with Beckman B spectrophotometer

The silicic acid used for chromatographic separation of *triglycerides, cholesterol and sterol esters* was prepared as described by HORNING *et al* (1960) When tested (O Haus Moisture Balance) the removable moisture percentage of silicic acid was found to be 9—12 per cent

The silicic acid column is prepared as follows Silicic acid is slurried in petroleum ether, poured into the column and allowed to settle under slight vibration of the column The height of the column is adjusted to 8—10 cm

The lipids remaining in the sublimation tube are dissolved in about one ml of petroleum ether This sample is pipetted onto the column and the test tube and the walls of the column are washed carefully with petroleum ether To protect the sample in the column, a layer, about ½ cm thick, of silicic acid petroleum ether is pipetted on the column as soon as the petroleum ether used for washing has disappeared into the column

Lipid fractions are eluted as follows

1) Sterol esters with 25 ml of 15 per cent (v/v) benzene petroleum ether

2) Cholesterol, triglycerides and diglycerides with 25 ml of chloroform

From these eluates (1 and 2) cholesterol is determined as follows

Aliquots of 10 ml are transferred with a pipette into round 25 ml flasks and evaporated to dryness with a rotating vacuum evaporator Flasks for method blank and cholesterol standard are added, and then 0 2 ml of distilled water 0 2 ml of glacial acetic acid is added to each flask except one into which is added 0 2 ml of cholesterol standard (containing 100 mg of cholesterol per 100 ml) After addition of 1 0 ml of p toluene sulphonic acid reagent the flasks are shaken, 3 0 ml of acetanhydride is added, and the contents of flasks are mixed rotating the flasks vigorously for 5 seconds After 25 minutes 0 4 ml of concentrated sulphuric acid is added and the flasks are shaken until a homogeneous mixture is achieved The colour is measured at 550 mµ in a Beckman B spectrophotometer after 20 minutes

Di and triglycerides (fraction 2) are determined as follows

Aliquots of 5 ml are evaporated to dryness in glass stoppered tubes 3 ml of Bloor's solution is added to each tube 1 0 ml of alkaline hydroxylamine reagent is added The rest of the procedure has been described earlier in connection with NEFA determination

Statistical methods

The degree of statistical significance has been determined by Student's t test The difference between two means is said to be significant if $0.01 < p \leqq 0.05$ highly significant if $0.001 < p \leqq 0.01$, and very highly significant if $p \leqq 0.001$

In the correlation studies, the correlation coefficient of Pearson was used The significance of the correlations was tested by the test variable

$$t = \sqrt{n-2} \quad \frac{r}{\sqrt{1-r}}$$

Fasting serum lipid values

Optical density

The mean values of the different groups are presented in Table 2

The mean value of males with diabetic heredity was about the same as that of diabetics and coronary patients They were somewhat higher than the mean value of the control subjects but no significant difference existed

Total lipids

The mean values are given in Table 3 Males with diabetic heredity showed a somewhat higher mean value than the controls whereas the means of diabetics and coronary patients were significantly higher than that of the control subjects When the upper normal limit was calculated as mean +2 S D of the control

TABLE 2 Serum optical density in fasting state at 650 mμ in different groups

	Control subject	Males with diabetic heredity	Diabetics	Coronary patients
Mean	119	139	141	14[illegible]
Range	[illegible]—280	[illegible]—470	80—370	[illegible]—[illegible]40
S D	±64	±89	±84	±113
S E M	±14	±19	±23	± [illegible]3
n	[illegible]	21	13	24
Statistical significance when compared with control subjects		N S	N S	N S

TABLE 3 Fasting serum total lipid values (mg per 100 ml) in different groups

	Control subject	Males with diabetic heredity	Diabetics	Coronary patients
Mean	[illegible]6	9[illegible]	83[illegible]	9[illegible]8
Range	[illegible]60—[illegible]	[illegible]—111[illegible]	[illegible]0—104[illegible]	[illegible]—1[illegible]
S D	±[illegible]	±1[illegible]3	±144	±[illegible]01
S E M	±21	± 38	± 40	± 41
n	[illegible]	21	13	[illegible]4
Statistical significance when compared with control subjects		N S	$p < 0.0[illegible]$	$p < 0.001$

methyl oleate standards of 1 μEq per 3 ml each and one method blank of 3 ml Bloor's solvent are added to the series. 1 ml of alkaline hydroxyl amine reagent is added, the tubes are sealed and allowed to stand 30 minutes in water bath (35—37 centigrade). Thereafter the tubes are cooled by running water and 0.5 ml of 3 n HCl is added. After mixing, 0.5 ml of $FeCl_3$ reagent is added, the tubes are shaken and after 30 minutes the samples are measured at 520 mμ with Beckman B spectrophotometer.

The silicic acid used for chromatographic separation of *triglycerides, cholesterol and sterol esters* was prepared as described by HOPKINS *et al.* (1960). When tested (O Haus Moisture Balance) the removable moisture percentage of silicic acid was found to be 9—12 per cent.

The silicic acid column is prepared as follows. Silicic acid is slurried in petroleum ether, poured into the column and allowed to settle under slight vibration of the column. The height of the column is adjusted to 8—10 cm.

The lipids remaining in the sublimation tube are dissolved in about one ml of petroleum ether. This sample is pipetted onto the column and the test tube and the walls of the column are washed carefully with petroleum ether. To protect the sample in the column, a layer, about ½ cm thick, of silicic acid petroleum ether is pipetted on the column as soon as the petroleum ether used for washing has disappeared into the column.

Lipid fractions are eluted as follows:

1) Sterol esters with 25 ml of 15 per cent (v/v) benzene petroleum ether.

2) Cholesterol, triglycerides and diglyceride with 25 ml of chloroform.

From these eluates (1 and 2) cholesterol is determined as follows:

Aliquots of 10 ml are transferred with a pipette into round 25 ml flasks and evaporated to dryness with a rotating vacuum evaporator. Flasks for method blank and cholesterol standard are added and then 0.2 ml of distilled water. 0.2 ml of glacial acetic acid is added to each flask except one into which is added 0.2 ml of cholesterol standard (containing 100 mg of cholesterol per 100 ml). After addition of 1.0 ml of p-toluene sulphonic acid reagent the flasks are shaken, 3.0 ml of acetanhydride is added and the contents of flasks are mixed rotating the flasks vigorously for 5 seconds. After 25 minutes 0.4 ml of concentrated sulphuric acid is added and the flasks are shaken until a homogeneous mixture is achieved. The colour is measured at 550 mμ in a Beckman B spectrophotometer after 20 minutes.

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Aliquots of 5 ml are evaporated to dryness in glass stoppered tubes. 3 ml of Bloor's solution is added to each tube. 1.0 ml of alkaline hydroxylamine reagent is added. The rest of the procedure has been described earlier in connection with NEFA determination.

Statistical methods

The degree of statistical significance has been determined by Student's t test. The difference between two means is said to be significant if $0.01 < p \leqq 0.05$, highly significant if $0.001 < p \leqq 0.01$ and very highly significant if $p \leqq 0.001$.

In the correlation studies the correlation coefficient of Pearson was used. The significance of the correlations was tested by the test variable

$$t = \sqrt{n-2} \cdot \frac{r}{\sqrt{1-r^2}}$$

diabetic heredity, there was a trend towards higher phospholipid values than in the control group, but the 95 per cent confidence level calculated from the control material was exceeded by none

Cholesterol, free and total

The mean values of free and total cholesterol are given in Tables 6 and 7

The males with diabetic heredity presented somewhat higher values than the control subjects but the difference was not statistically significant In diabetics the free cholesterol content was significantly higher than in the controls The mean value of total cholesterol was also clearly, though not significantly, higher than in the control group ($p = 0.09$) The cholesterol was determined in only 10 coronary patients, it was considered that ample data on this parameter were available from earlier investigations As expected the coronary group showed significantly higher mean values of both free and total cholesterol than did the control subjects

Non esterified fatty acids

The mean values are presented in Table 8

The diabetics had higher mean values than the control subjects, but the dif

TABLE 6 Fasting values of serum free cholesterol (mg per 100 ml) in different groups

	Control subjects	Males with diabetic heredity	Diabetics	*Coronary* patients
Mean	6[illegible]	66	74	97
Range	36—93	40—97	50—113	38—127
S D	±14	±18	±19	±21
S E M	± 3	± 4	± 6	± 6
n	22	19	11	10
Statistical significance when compared with *control subjects*		NS	$p < 0.05$	$p < 0.001$

TABLE 7 Fasting values of serum total cholesterol (mg per 100 ml) in different groups

	Control subjects	Males with diabetic heredity	Diabetics	Coronary patients
Mean	1[illegible]8	199	20[illegible]	[illegible]64
Range	105—271	130—258	143—243	193—344
S D	±4[illegible]	±4[illegible]	±46	±48
S E M	± 9	±10	±14	±15
n	[illegible]1	19	11	10
Statistical significance when compared with control subjects		NS	NS	$p < 0.001$

group (representing 95 per cent confidence limit), it was found that this value, 1056 mg per cent, was exceeded by none of the control subjects and no diabetics, by two males with diabetic heredity (9 per cent), and by seven coronary patients (29 per cent).

Triglycerides

The mean values of the various groups are given in Table 4.

Untreated diabetics and coronary patients had significantly higher mean values than the control subjects or males with diabetic heredity. The mean value for males with diabetic heredity was the *only lipid fraction which was slightly lower than the mean for the controls.* — *The 95 per cent confidence level was exceeded by one control subject* (5 per cent), by one male with diabetic heredity (5 per cent), by three diabetics (23 per cent), *and by four coronary patients* (17 per cent).

Lipid phosphorus

The mean values are presented in Table 5.

The lipid phosphorus was determined in only 14 coronary patients, their mean value was significantly higher than that of the control subjects. In males with

TABLE 4. Fasting serum triglyceride values (mEq per 1) in different groups

	Control subjects	Males with diabetic heredity	Diabetics	Coronary patients
Mean	5.62	5.33	7.22	6.81
Range	3.2—9.1	2.4—9.1	4.4—10.7	3.8—10.4
S.D.	±1.67	±1.78	±1.95	±1.93
S.E.M.	±0.36	±0.39	±0.54	±0.39
n	22	21	13	24
Statistical significance when compared with control subjects		NS	$p < 0.05$	$p < 0.05$

TABLE 5. Fasting values of serum lipid phosphorus (mg per 100 ml) in different groups

	Control subjects	Males with diabetic heredity	Diabetics	Coronary patients
Mean	8.48	9.28	9.54	9.70
Range	5.6—11.8	5.3—12.0	7.5—15.1	6.8—12.1
S.D.	±1.82	±2.08	±2.17	±1.55
S.E.M.	±0.39	±0.45	±0.57	±0.43
n	22	21	13	14
Statistical significance when compared with control subjects		NS	NS	$p < 0.05$

diabetic heredity, there was a trend towards higher phospholipid values than in the control group, but the 95 per cent confidence level calculated from the control material was exceeded by none

Cholesterol free and total

The mean values of free and total cholesterol are given in Tables 6 and 7

The males with diabetic heredity presented somewhat higher values than the control subjects but the difference was not statistically significant In diabetics the free cholesterol content was significantly higher than in the controls The mean value of total cholesterol was also clearly, though not significantly, higher than in the control group ($p \approx 0.09$) The cholesterol was determined in only 10 coronary patients, it was considered that ample data on this parameter were available from earlier investigations As expected the coronary group showed significantly higher mean values of both free and total cholesterol than did the control subjects

Non esterified fatty acids

The mean values are presented in Table 8

The diabetics had higher mean values than the control subjects but the dif

TABLE 6 Fasting values of serum free cholesterol (mg per 100 ml) in different groups.

	Control subjects	Males with diabetic heredity	Diabetics	Coronary patients
Mean	62	66	74	97
Range	36—93	40—9[illegible]	50—113	38—127
S D	±14	±18	±19	±21
S E M	± 3	± 4	± 6	± 6
n	22	19	11	10
Statistical significance of mean compared with control subjects		NS	$p < 0.05$	$p < 0.001$

TABLE 7 Fasting values of serum total cholesterol (mg per 100 ml) in different groups.

	Control subjects	Males with diabetic heredity	Diabetics	Coronary patients
Mean	178	199	20[illegible]	264
Range	105—[illegible]1	130—259	143—248	193—344
S D	±42	±45	±46	±48
S E M	± 9	±10	±14	±15
n	[illegible]	19	11	10
Statistical significance of mean compared with control subjects		NS	NS	$p < 0.001$

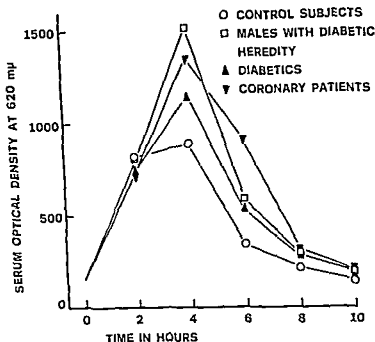
TABLE 8 Fasting values of serum non esterified fatty acids (mEq per l) in different groups

	Control subjects	Males with diabetic heredity	Diabetics	Coronary patients
Mean	0.301	0.322	0.406	0.342
Range	0.05—0.75	0.12—0.72	0.19—0.83	0.16—0.70
S D	±0.147	±0.148	±0.177	±0.146
S E M	±0.032	±0.032	±0.049	±0.030
n	21	21	13	23
Statistical significance when compared with control subjects		NS	NS	NS

TABLE 9 *Serum optical density* (at 620 mμ) in different groups during the fat loading test

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	119	815	885	345	212	145
Range	65—280	115—1890	305—2050	115—605	100—400	65—250
S D	±64	±445	±516	±180	±58	±47
S E M	±14	± 95	±110	± 38	±19	±10
n	22	22	22	22	22	22
Males with diabetic heredity						
Mean	139	810	1512**	585*	275	194
Range	*55—470*	*95—1925*	*225—2500*	*135—2060*	*70—700*	*55—415*
S D	±59	±549	±710	±411	±172	±98
S E M	±19	±117	±153	± 90	± 37	±21
n	21	22	21	22	22	21
Diabetics						
Mean	141	836	1141	528*	270	175
Range	80—330	300—1750	465—2500	310—1010	150—510	105—325
S D	±84	±478	±530	±214	±100	±75
S E M	±23	±133	±153	± 59	± 29	±22
n	13	13	12	13	12	12
Coronary patients						
Mean	142	720	1350*	901	312	200
Range	55—540	125—1730	*210—2500*	*105—2500*	*130—815*	*110—390*
S D	±113	±539	±652	±645	±171	±93
S E M	±23	±108	±136	±129	± 46	±27
n	24	25	25	25	14	12

Statistical significance when compared with control subjects
* $p < 0.05$, ** $p < 0.01$ *** $p < 0.001$



F g 1 Me n alu s of se um op cal de y du ng the fat load ng te t n l ff nt groups.

fere e as t t ti t eally s g ficant (p)(7 Tl e r ean valu s of males tl d abet heredit and coronary pa t ents ere also one vlat higher as pared th contr l s bjects.

Serum lipid values after the fat load

Opt l l s ty

Tl a al s t the l ff r t h l l 4 6 S a l 10 hours after tl fat load are pres t l i Tall l and F 1

N fi ant l ff re es ere se t t l rs ft r the fat loa l altl o l l a l f tl x t are group as l at l r tl a tl t e s for l tl r tl ree gro p

I l s ft r tl f t load tl re was lo ever a significant difference bet een the mean values of males vith l abet e heredity and coronary patients on the one hand and the control subjects on the other The first t o groups exhibited significantly higher mean values than the control subjects The diabetics also had a higher mean value than the control subjects In all groups the highest mean value of optical density as reached at this point The 95 per ent confidence level calculated from the an val e in the c trol group as exceeded l one control subject per ent) l v ne males with diabetic heredity (43 p r c nt) l y one diabetic S per cent) a l l y se en coronary pat t (S per cent) The males with l abet c heredity a l the coronary pa

TABLE 8 Fasting values of serum non esterified fatty acids (mEq per l) in different groups

	Control subjects	Males with diabetic heredity	Diabetics	Coronary patients
Mean	0.301	0.322	0.406	0.34[illegible]
Range	0.05—0.75	0.12—0.72	0.19—0.83	0.16—0.70
S D	±0.147	±0.148	±0.177	±0.146
S E M	±0.032	±0.032	±0.049	±0.030
n	21	21	13	23
Statistical significance when compared with control subjects		NS	NS	NS

TABLE 9 *Serum optical density* (at 620 mμ) in different groups during the fat loading test

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	119	815	885	345	212	145
Range	65—280	115—1890	305—2050	115—605	100—400	65—250
S D	±64	±445	±516	±180	±88	±47
S E M	±14	± 95	±110	± 38	±19	±10
n	22	22	22	22	22	22
Males with diabetic heredity						
Mean	139	810	1512**	585*	278	194
Range	55—470	95—1925	225—2500	135—2060	70—700	55—415
S D	±89	±519	±710	±411	±172	±93
S E M	±19	±117	±155	± 90	± 37	±21
n	21	22	21	22	22	21
Diabetics						
Mean	141	836	1141	528*	270	175
Range	80—330	400—1750	465—2500	310—1010	150—510	105—325
S D	±84	±478	±530	±214	±100	±75
S E M	±23	±133	±153	± 59	± 29	±22
n	13	13	12	13	12	12
Coronary patients						
Mean	142	720	1350*	901*	312*	200*
Range	55—540	125—1730	210—2500	105—2500	130—815	110—390
S D	±113	±539	±682	±645	±171	±93
S E M	±23	±108	±136	±129	± 46	±27
n	24	25	25	25	14	12

Statistical significance when compared with control subjects
* $p < 0.05$, ** $p < 0.01$ *** $p < 0.001$

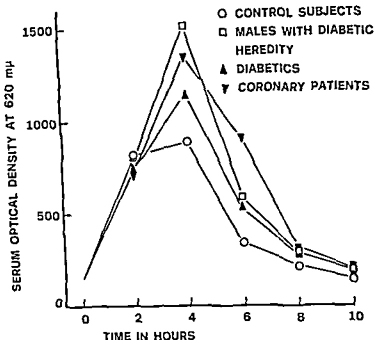


Fig 1 Mean values of serum optical density during the fat loading test in different groups

ference was not statistically significant ($p = 0.07$) The mean values of males with diabetic heredity and coronary patients were also somewhat higher as compared with control subjects

Serum lipid values after the fat load

Optical density

The mean values in the different groups 0 2 4 6 8 and 10 hours after the fat load are presented in Table 9 and Fig 1

No significant differences were seen two hours after the fat load although the mean value for the coronary group was somewhat lower than the means for the other three groups

Four hours after the fat load there was however a significant difference between the mean values of males with diabetic heredity and coronary patients on the one hand and the control subjects on the other The first two groups exhibited significantly higher mean values than the control subjects The diabetics also had a higher mean value than the control subjects In all groups the highest mean value of optical density was reached at this point The 95 per cent confidence level calculated from the mean value in the control group was exceeded by one control subject (5 per cent) by nine males with diabetic heredity (43 per cent) by one diabetic (8 per cent) and by seven coronary patients (28 per cent) The males with diabetic heredity and the coronary pa

tients thus seemed to respond similarly to a fat load judged by the four hour serum optical density value

Six hours after the fat load the mean values in all the groups were lower than four hours after it Compared with the control group the mean values in the coronary group was still much greater the difference being very highly significant but the mean values of males with diabetic heredity and diabetics were also significantly higher The 95 per cent confidence level calculated from the mean value of the control group was exceeded by one control subject (5 per cent) by seven males with diabetic heredity (32 per cent) by the diabetics (23 per cent) and by 14 coronary patients (56 per cent)

Eight hours and ten hours after the fat load the mean values of coronary patients were still significantly higher than those of the control subjects There was no significant difference between

TABLE 10 *Serum total lipids* (mg per 100 ml) in different groups during the fat loading test

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	[illegible]	834	831	[illegible]	[illegible]	[illegible]
Range	560—935	[illegible]	605—1155	[illegible]—1045	[illegible]	510—1030
S D	[illegible]	±145	±147	[illegible]	±133	±134
S E M	[illegible]	± 31	± 31	[illegible]	[illegible]	± 30
n	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Males with diabetic heredity						
Mean	[illegible]	[illegible]	1046***	[illegible]	844*	814*
Range	545—1115	590—1455	[illegible]	560—1315	565—1090	530—1135
S D	[illegible]	[illegible]	[illegible]	±211	±165	±183
S E M	± 38	± 46	± 51	± 45	± 35	± 39
n	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Diabetics						
Mean	[illegible]	948	1015**	[illegible]	[illegible]	833
Range	590 1045	[illegible]	[illegible]	550—1405	530—1090	550—1095
S D	±144	±188	[illegible]	±218	[illegible]	±181
S E M	± 40	± 54	[illegible]	± 61	± 51	[illegible]
n	13	13	[illegible]	13	[illegible]	[illegible]
Coronary patients						
Mean	[illegible]	[illegible]	1138***	[illegible]	958*	906**
Range	[illegible]	[illegible]	[illegible]	455—1495	[illegible]	385—1130
S D	[illegible]	[illegible]	[illegible]	±259	[illegible]	[illegible]
S E M	± 41	± 45	[illegible]	[illegible]	± 65	± 67
n	[illegible]	[illegible]	[illegible]	[illegible]	14	[illegible]

Statistical significance when compared with control subjects
$^{*}p < 0.05$ $^{**}p < 0.01$ $^{***}p < 0.001$

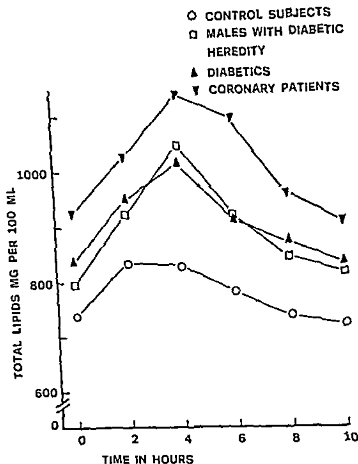


Fig. 2. Mean values of serum total lipids during the fat loading test in different groups.

the control subjects and males with diabetic heredity or the diabetics, although the mean values of the latter two groups were somewhat higher.

Total lipids

The mean values of total lipids obtained after fat loading in different groups are presented in Table 10 and Fig. 2.

The mean value two hours after the fat load was only in the coronary group significantly higher than in control subjects. Four hours after the fat load it was significantly greater in all the three clinical groups than in control subjects. The 95 per cent confidence level, calculated from the control material, was 1125 mg per cent. This was exceeded by one control subject (5 per cent), by eight males with diabetic heredity (38 per cent), by three diabetics (25 per cent) and by 15 coronary patients (60 per cent).

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Six hours after the fat load the mean values in all the groups were lower than four hours after it Compared with the control group, the mean values in the coronary group was still much greater, the difference being very highly significant, but the mean values of males with diabetic heredity and diabetics were also significantly higher The 95 per cent confidence level, calculated from the mean value of the control group was exceeded by one control subject (5 per cent) by seven males with diabetic heredity (32 per cent), by three diabetics (23 per cent), and by 14 coronary patients (56 per cent)

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TABLE 10 Serum total lipids (mg per 100 ml) in different groups during the fat loading test

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	726	834	831	80	736	--
Range	560—935	555—1120	605—1155	575—1045	5[illegible]5—1075	510—1030
S D	±97	±145	±147	±128	±133	±134
S E M	±21	± 31	± 31	± [illegible]7	+ 29	± 30
n	22	22	22	[illegible]2	21	20
Males with diabetic heredity						
Mean	97	922	1046***	921**	844*	814*
Range	545—1115	590—1455	5[illegible]0—1485	560—1315	565—1090	530—1135
S D	±1[illegible]3	±210	±235	±211	±165	±183
S E M	± 38	± 46	± 51	± 45	± 35	± 39
n	21	21	21	22	[illegible]2	[illegible]2
Diabetics						
Mean	937**	948	1015**	912*	8[illegible]0*	833
Range	590—1045	560—1260	605—14[illegible]0	550—1405	530—1090	550—1095
S D	±144	+188	±241	±218	±170	±181
S E M	+ 40	± 54	± [illegible]0	+ 61	± 51	± 52
n	13	13	12	13	1[illegible]	12
Coronary patients						
Mean	9[illegible]8**	1023*	1138	1092***	955*	906**
Range	5[illegible]5—1[illegible]85	6[illegible]0—1340	1[illegible]5—1565	455—1495	400—1245	385—1170
S D	±201	+2[illegible]3	±233	±259	±[illegible]44	±232
S E M	+ 41	± 45	± 47	± 52	± 65	± 67
n	[illegible]4	25	[illegible]5	[illegible]5	14	12

Statistical significance when compared with control subjects
$^{*} p < 0.05$ $^{**} p < 0.01$ $^{***} p < 0.001$

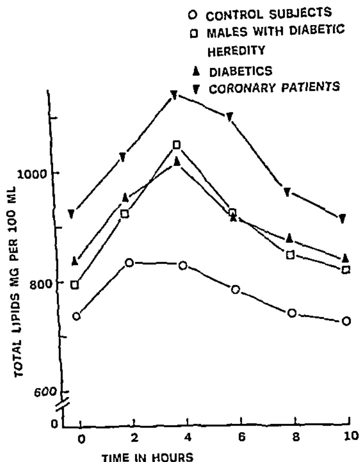

Fig 2 Mean values of serum total lipids during the fat loading test in different groups

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Total lipids

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The mean value two hours after the fat load was only in the coronary group significantly higher than in control subjects Four hours after the fat load it was significantly greater in all the three clinical groups than in control subjects The 95 per cent confidence level calculated from the control material was 1125 mg per cent This was exceeded by one control subject (5 per cent) by eight males with diabetic heredity (38 per cent) by three diabetics (25 per cent) and by 15 coronary patients (60 per cent)

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Eight hours and ten hours after the fat load the mean values of coronary patients were still significantly higher than those of the control subjects There was no significant difference between

TABLE 10 *Serum total lipids* (mg per 100 ml) in different groups during the fat loading test

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	7[illegible]6	834	831	780	736	[illegible]2
Range	560—935	555—1120	605—1155	5 5—1045	525—10 5	510—1030
S D	±9	±145	±147	±128	±133	±134
S E M	±21	± 31	± 31	[illegible]	± 29	± 30
n	[illegible]	22	22	22	21	20
Males with diabetic heredity						
Mean	797	922	1046***	921**	841*	814*
Range	545—1115	590—1455	5 0—1485	560—1315	565—1090	530—1135
S D	±1 5	±210	±235	±211	±165	±183
S E M	± 38	± 46	± 51	± 45	± 35	± 39
n	21	21	21	22	22	22
Diabetics						
Mean	83 *	948	1015**	91[illegible]*	8 0*	833
Range	590—1045	560—1260	605—1470	550—1405	530—1090	550—1095
S D	±144	±188	±241	±218	±170	±181
S E M	± 40	± 54	± 0	± 61	± 51	± 52
n	13	13	12	13	12	12
Coronary patients						
Mean	928***	1023**	1138 *	1092* *	9[illegible]5 *	906**
Range	575—1 85	620—1340	715—1565	455—1495	400—1 45	385—1130
S D	±201	±223	±233	±259	±[illegible]44	±232
S E M	± 41	± 45	± 4	± 52	± 65	± 67
n	[illegible]4	[illegible]5	25	[illegible]5	14	12

Statistical significance when compared with control subjects
* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

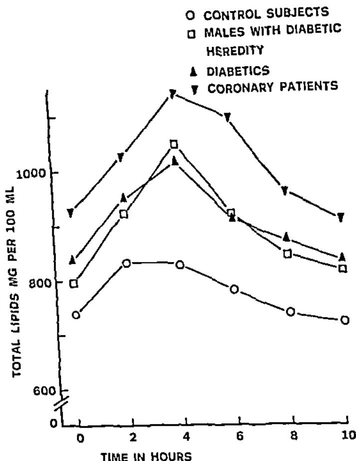

Fig 2 Mean values of serum total lipids during the fat loading test in different groups.

the control subjects and males with diabetic heredity or the diabetics although the mean values of the latter two groups were somewhat higher

Total lipids

The mean values of total lipids obtained after fat loading in different groups are presented in Table 10 and Fig 2

The mean value two hours after the fat load was only in the coronary group significantly higher than in control subjects Four hours after the fat load it was significantly greater in all the three clinical groups than in control subjects The 95 per cent confidence level, calculated from the control material was 1125 mg per cent This was exceeded by one control subject (5 per cent) by eight males with diabetic heredity (38 per cent) by three diabetics (25 per cent) and by 15 coronary patients (60 per cent)

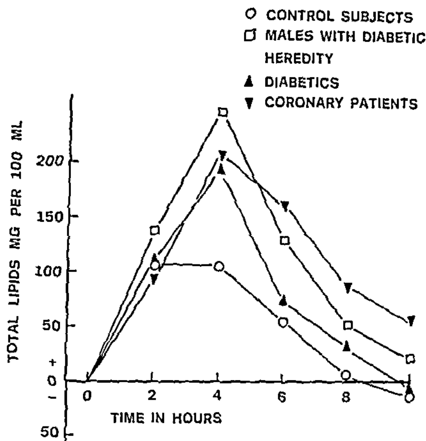

Fig 3 Absolute changes in serum total lipids during the fat loading test in different groups

Six hours after the fat load the mean values for the three test groups were significantly higher than in the control subjects The 95 per cent confidence level, 1036 mg per cent, was exceeded by one control subject (5 per cent) by seven males with diabetic heredity (32 per cent) by three diabetics (23 per cent) and by 17 coronary patients (68 per cent) It was observed that seven out of eight males with diabetic heredity the three diabetics, and 15 out of 17 coronary patients were included among those who had high total lipid values four hours after the fat load Thus the determination of total lipids both four and six hours after the fat load did not substantially increase the number of abnormal values as compared with total lipid values four hours or six hours after the fat load

Eight hours after fat ingestion the mean values of total lipids in the three test groups were still significantly higher than in the control subjects This also applies to males with diabetic heredity and with coronary disease ten hours after the fat load

In order to facilitate the comparison of different groups the two-hourly changes of total lipids have also been calculated taking the fasting level as zero value (Fig 3) The change from two-hour level to four-hour level was

much greater (the difference very highly significant) in males with diabetic heredity and in coronary patients than in control subjects. In diabetics too this change was significantly ($p < 0.05$) greater than in controls. The drop from four hour level to six hour level was greatest in diabetics and males with diabetic heredity. After that the changes in the various groups did not differ very much.

Triglycerides

The mean values in the different groups during the fat loading test are presented in Table 11 and Fig. 4.

Two hours after the fat load the mean values for the control subjects and males with diabetic heredity were equal, whereas those obtained for coronary patients and diabetics were higher. Owing to the wide range of individual values in the latter group the mean value was not

TABLE 11. *Serum triglycerides* (mEq per l) in different groups during the fat loading test.

	0 hrs	2 hr	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	5 62	7.20	7 04	5 75	4 67	4 97
Range	3 2—9 1	3 6—11 6	3 6—12 5	2 8—10 0	2 6—8 8	2 3—7 9
S D	±1 67	±1 93	±2 20	±2 09	±1 81	±1 8[illegible]
S E M	±0 36	±0 42	±0 47	±0 44	±0 39	±0 49
n	22	21	22	22	21	14
Males with diabetic heredity						
Mean	5 35	7 24	9 16	6 89	5 72	5 14
Range	2 4—9 1	3 9—11 0	4 3—13 9	2 8—12.5	2 6—10 1	2.6—9.2
S D	±1 78	±2 04	±2 62	±2 41	±1 86	±1.59
S E M	±0 39	±0 47	±0 59	±0 54	±0 41	±0 41
n	21	19	20	22	22	21
Diabetics						
Mean	[illegible]22	9 12	10 07	8 45	6 48	5 94
Range	4 4—10 7	4 3—15 7	5 2—16 7	3 9—13 0	3 6—10 1	3 6—10 1
S D	±1 95	±3 78	±3 2	±3 10	±2 4[illegible]	±1 79
S E M	±0 54	±1 05	±0 94	±0 86	±0 70	±0 54
n	13	13	12	13	12	11
Coronary patients						
Mean	6 91	8 65	10 84*	10 14	7 29 *	6 04
Range	3 8—10 4	4 8—13 7	6 2—16 2	4 9—18 0	4 1—12 1	3 9—8 7
S D	±1 93	±2 42	±3 61	±3 [illegible]7	±2 29	±1 54
S E M	±0 39	±0 48	±0 72	±0 75	±0 61	±0 45
n	24	25	25	25	14	12

Statistical significance when compared with control subjects
$p < 0.05$ $p < 0.01$ $p < 0.001$

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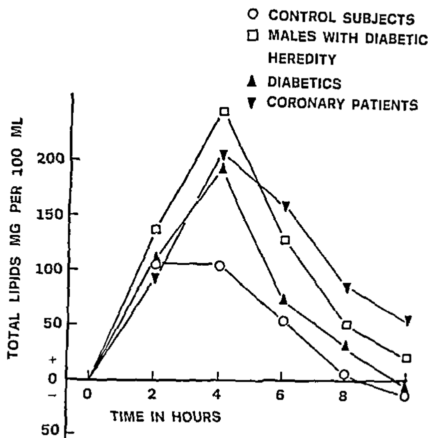

Fig 3 Absolute changes in serum total lipids during the fat loading test in different groups

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Eight hours after fat ingestion the mean values of total lipids in the three test groups were still significantly higher than in the control subjects This also applies to males with diabetic heredity and with coronary disease ten hours after the fat load

In order to facilitate the comparison of different groups the two hourly changes of total lipids have also been calculated taking the fasting level as zero value (Fig 3) The change from two hour level to four hour level was

much greater (the difference very highly significant) in males with diabetic heredity and in coronary patients than in control subjects. In diabetics too this change was significantly ($p < 0.05$) greater than in controls. The drop from four hour level to six hour level was greatest in diabetics and males with diabetic heredity. After that the changes in the various groups did not differ very much.

Triglycerides

The mean values in the different groups during the fat loading test are presented in Table 11 and Fig. 4.

Two hours after the fat load the mean values for the control subjects and males with diabetic heredity were equal whereas those obtained for coronary patients and diabetics were higher. Owing to the wide range of individual values in the latter group, the mean value was not

TABLE 11. *Serum triglycerides* (mEq per l) in different groups during the fat loading test

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	5.62	7.20	7.04	5.75	4.67	4.97
Range	3.2—9.1	3.6—11.6	3.6—12.5	2.8—10.0	2.6—9.8	2.3—7.9
S.D.	±1.6[illegible]	±1.93	±2.20	±2.09	±1.81	±1.5[illegible]
S.E.M.	±0.36	±0.42	±0.47	±0.44	±0.39	±0.49
n	22	21	22	[illegible]	[illegible]	14
Males with diabetic heredity						
Mean	5.35	7.24	9.16	6.89	[illegible]	5.14
Range	2.4—9.1	3.9—11.0	4.3—13.9	2.8—1[illegible].5	2.6—10.1	2.6—9.2
S.D.	±1.[illegible]8	±2.04	±2.62	±2.41	±1.86	±1.89
S.E.M.	±0.39	±0.4[illegible]	±0.59	±0.54	±0.41	±0.41
n	21	19	20	[illegible]	22	21
Diabetics						
Mean	[illegible]	9.12	10.0[illegible]*	8.45	6.48	5.94
Range	4.4—10.[illegible]	4.3—15.[illegible]	5.2—16.7	3.9—13.0	3.6—10.1	3.6—10.1
S.D.	±1.95	±3.78	±3.27	±3.10	±2.42	±1.[illegible]9
S.E.M.	±0.54	±1.05	±0.94	±0.86	±0.[illegible]0	±0.54
n	13	13	12	13	12	11
Coronary patients						
Mean	6.81	8.65	10.84	10.14 *	7.29	6.04
Range	3.8—10.4	4.8—13.7	6.2—16.2	4.9—18.0	4.1—12.1	3.9—8.[illegible]
S.D.	±1.93	±2.42	±3.61	±3.[illegible]7	±2.29	±1.54
S.E.M.	±0.39	±0.48	±0.[illegible]2	±0.[illegible]5	±0.61	±0.45
n	[illegible]4	25	25	25	14	1[illegible]

Statistical significance when compared with control subjects:
$p < 0.05$ $p < 0.01$ $p < 0.001$

3

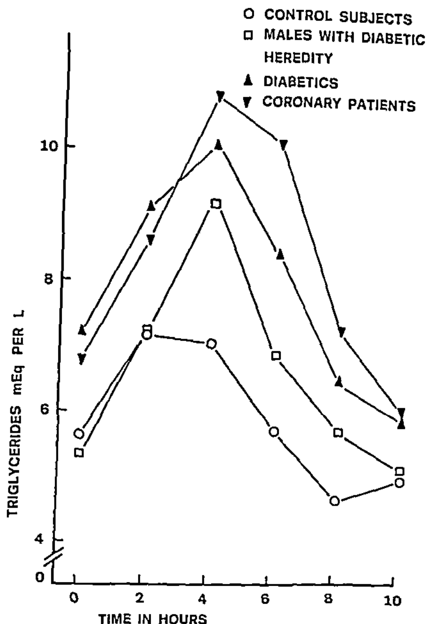


Fig 4 Mean values of serum triglycerides during the fat loading test in different groups

significantly different from that of control subjects

Four hours after the administration of fat all the three test groups exhibited mean values higher than those for the controls In males with diabetic heredity and in diabetics the difference (compared with control subjects) was statistically highly significant and in the coronary group very highly significant The 95 per cent confidence level calculated from the mean of control subjects was 11 24 mEq per l This value was exceeded by one control subject (5 per cent) by five males with diabetic heredity (25 per cent), by four diabetics

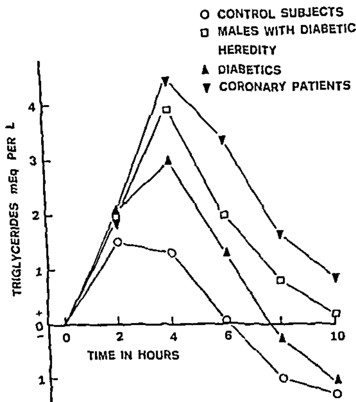


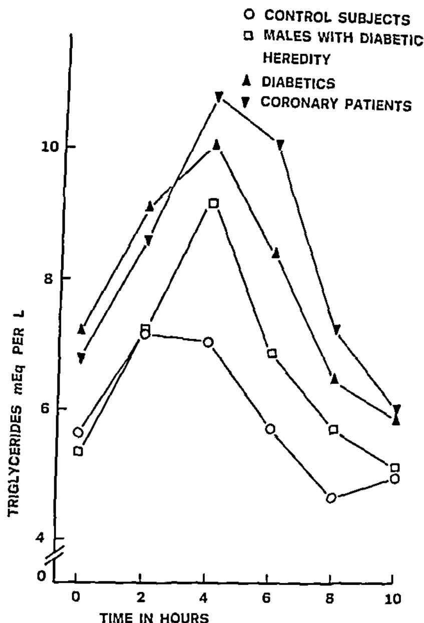
Fig 5 Absolute changes in serum triglycerides during the fat loading test in different groups

(33 per cent) and by 13 coronary patients (52 per cent)

Six hours after the fat load all groups showed lower mean values than four hours after the fat load The mean value of males with diabetic heredity was somewhat higher than that of the controls but the difference was not significant Diabetics and coronary patients still had significantly higher mean values than the control subjects The 95 per cent confidence level 9 93 mEq per l calculated from the mean value of controls was exceeded by one control subject (5 per cent) by only two males with diabetic heredity (9 per cent), by four diabetics (31 per cent), and by 11 coronary patients (44 per cent) All these subjects except the control subject and one diabetic, were already separated out by the high four hour value

The mean values eight hours after the fat load were significantly higher in diabetics and coronary patients compared with the controls The mean value of males with diabetic heredity was somewhat although not significantly higher than that of the control group

Ten hours after the fat load there were no significant differences The



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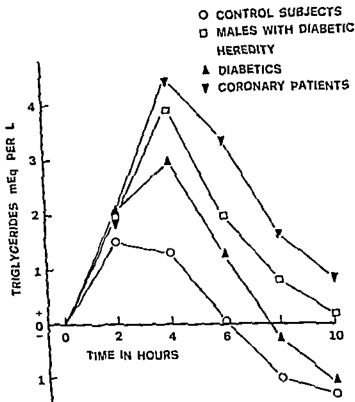

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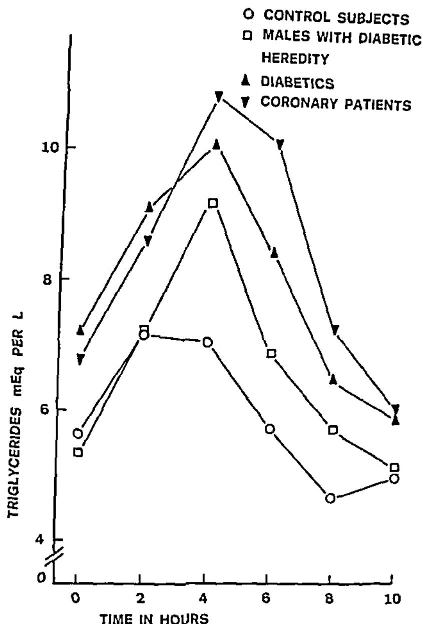

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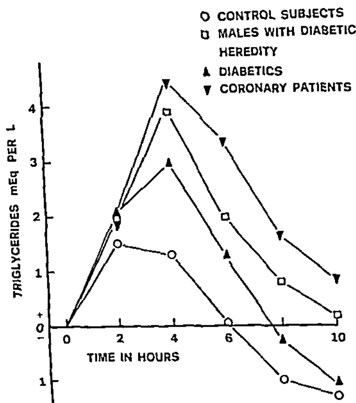

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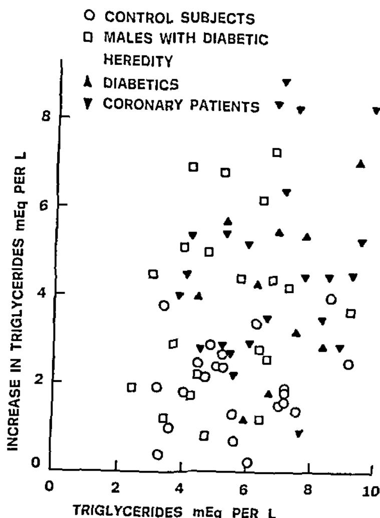

Fig. 6 Relationship of fasting serum triglyceride level and maximal increase in triglyceride level, two, four or six hours after the fat load. Correlation coefficients and t values in different groups

Control subjects	r = +0.15	t = 0.656
Males with diabetic heredity	r = −0.01	t = 0.028
Diabetics	r = +0.15	t = 0.074
Coronary patients	r = +0.28	t = 1.440

mean values in all the four groups were already lower than the fasting values. It was observed, however, that the ten hour value was higher than the fasting value in nine males with diabetic heredity as compared to one control subject.

Fig. 5 shows the two hourly changes in triglycerides in the different groups, taking the fasting level as zero value.

The changes from two hour level to four hour level were similar in males with diabetic heredity and in coronary patients, being significantly greater ($p < 0.001$) than in control subjects. Owing to great individual variations the change in diabetics was not significantly different from that obtained for controls, although a rise was observed.

The drop from four hour level to six

hour level was great in males with diabetic heredity, i e more than double the value recorded for coronary patients, who exhibited the smallest drop of all four groups

Significant changes as compared to controls occurred neither from the six hour to eight hour level nor from the eight hour to ten hour level

Fig 6 shows the relationship between the fasting triglyceride values and the maximal increase recorded either two, four or six hours after the fat load

No significant correlation was found in any of the four groups The highest r value 0 28, was recorded in coronary patients.

Lipid phosphorus

The mean values for the different groups after fat loading are given in Table 12 and Fig 7

Table 12 *Serum lipid phosphorus (mg per 100 ml) in different groups during the fat loading test*

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	8 48	8 58	9 30	9 01	8 88	8 82
Range	5 6—11 8	5 7—12.5	6 2—13 0	5 8—12 8	5 1—12.5	5.3—12 1
S D	±1 82	±1 95	±1 90	±1 79	±1 79	±1 84
S E M	±0 39	±0 42	±0 40	±0 38	±0.38	±0 41
n	2[illegible]	22	22	22	22	20
Males with diabetic heredity						
Mean	9 28	9 80	10 26	10 [illegible]0	9 99	9 73
Range	5 3—12 0	5 9—13.5	5 9—12.3	6 1—15.5	5 6—14 9	6.5—15 4
S D	±2 08	±1 89	±2 00	±2 [illegible]	±[illegible]06	±[illegible]26
S E M	±0 45	±0 41	±0 44	±0 44	±0 44	±0 48
n	21	21	[illegible]1	[illegible]2	22	22
Diabetics						
Mean	9 54	10 22	10 12	9 96	9 63	9 67
Range	5—15 1	7 6—14 8	6 9—15 5	[illegible] 4—14 1	6 6—13 5	6 4—15 1
S D	±[illegible] 17	±2 26	±2 33	±1 80	±1.99	±[illegible]
S E M	±0 5[illegible]	±0 63	±0 67	±0 50	±0 5[illegible]	±0 66
n	13	13	12	13	12	12
Coronary patients						
Mean	9 [illegible]0	10 34	11 06	10 93	10 75	10.38*
Range	[illegible] 8—[illegible]	[illegible] 4—12.9	8 4—13 5	8.5—13 5	8 2—13 7	6 [illegible]—12 9
S D	±1 55	±1 62	±1 46	±1 58	±1 62	±1.94
S E M	±0 43	±0 43	±0 39	±0 42	±0 43	±0.56
n	13	14	14	14	14	12

Statistical significance when compared with control subjects

p < 0 05   p < 0 01   p < 0 001

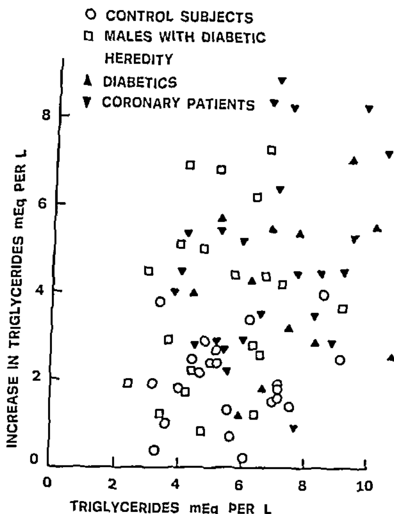

Fig 6 Relationship of fasting serum triglyceride level and maximal increase in triglyceride level, two, four or six hours after the fat load Correlation coefficients and t values in different groups

Control subjects	r = +0.13	t = 0.686
Males with diabetic heredity	r = −0.01	t = 0.028
Diabetics	r = +0.15	t = 0.074
Coronary patients	r = +0.28	t = 1.440

mean values in all the four groups were already lower than the fasting values It was observed, however, that the ten hour value was higher than the fasting value in nine males with diabetic heredity as compared to one control subject

Fig 5 shows the two hourly changes in triglycerides in the different groups, taking the fasting level as zero value

The changes from two hour level to four hour level were similar in males with diabetic heredity and in coronary patients, being significantly greater ($p < 0.001$) than in control subjects Owing to great individual variations the change in diabetics was not significantly different from that obtained for controls although a rise was observed

The drop from four hour level to six

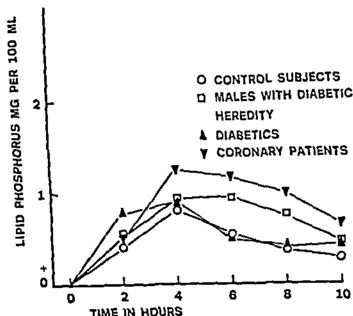

Fig 8 Absolute changes in serum lipid phosphorus during the fat loading test in different groups

(5 per cent) one diabetic (8 per cent) and by three coronary patients (21 per cent)

Fig 8 shows the two-hourly changes in lipid phosphorus in different groups taking the fasting level as zero value

No significant differences appeared between the two hourly changes in the various groups The greatest rise from the fasting to four hour level was observed in the coronary patients but the changes in the other three groups were nearly equal

Cholesterol free and total

The mean free cholesterol values after fat loading are presented in Table 13 and Fig 9

The mean values of free cholesterol in the different groups did not change significantly during the fat loading test It was interesting to note, however, that the value four hours after the fat load was smaller than the fasting value in 13 control subjects (59 per cent), in only four males with diabetic heredity (21 per cent) in three diabetics (30 per cent) and in three coronary patients (30 per cent) This explains the observation that four hours after the fat load the mean values for males with diabetic heredity and diabetics, were significantly greater than in control subjects In addition the mean values for diabetics six hours after the fat load and the means of both diabetics and males with diabetic heredity eight hours after the fat load were significantly greater than in the control group At

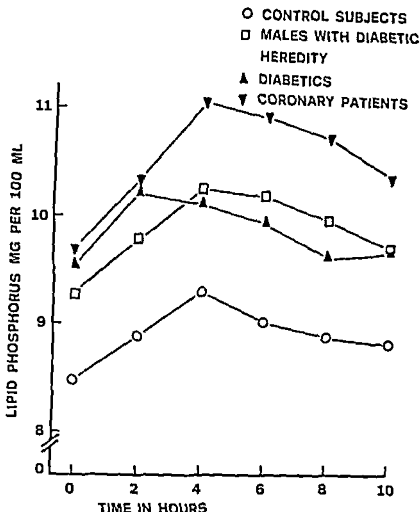

Fig. 7 Mean values of serum lipid phosphorus during the fat loading test in different groups

The mean levels of the three test groups during the fat loading test were higher than those of control subjects at each sampling point In males with diabetic heredity the only statistically significant difference as compared with controls was observed six hours after the fat load, whereas the mean levels of diabetics were not significantly higher The coronary patients had, at each sampling point, significantly higher mean values than the control subjects The lowest p value was recorded four, six, and eight hours after the fat load

The 95 per cent confidence level, calculated from the mean control value, was exceeded, four hours after the fat load, by one control subject (5 per cent) by none of the males with diabetic heredity, by only one diabetic (8 per cent) and one coronary patient (7 per cent) Six hours after the fat load it was exceeded by one control subject (5 per cent), one male with diabetic heredity

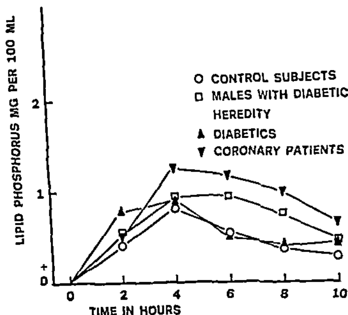

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Table 13 *Free serum cholesterol (mg per 100 ml) in different groups during the fat loading test*

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	62	62	60	60	57	56
Range	36—93	41—95	35—100	39—97	38—90	33—88
S D	±14	±16	±14	±15	±14	±16
S E M	± 3	± 3	± 3	± 3	± 3	± 4
n	22	22	22	22	22	13
Males with diabetic heredity						
Mean	66	71	74**	68	67*	62
Range	40—97	43—123	44—108	40—85	45—89	34—8[illegible]
S D	±18	±18	±18	±14	±12	±13
S E M	± 4	± 4	± 4	± 3	± 3	± 3
n	19	19	19	20	20	20
Diabetics						
Mean	74*	70	75*	73*	66*	64
Range	50—113	50—93	50—111	48—98	45—84	47—84
S D	±19	±16	±18	±15	±12	±13
S E M	± 6	± 6	± 6	± 4	± 4	± 4
n	11	8	10	11	10	9
Coronary patients						
Mean	97***	94***	98***	97***	95***	94***
Range	69—1[illegible]7	62—139	78—12[illegible]	69—119	69—112	74—120
S D	±21	±23	±14	±17	±14	±14
S E M	± 6	± 7	± 4	± 5	± 5	± 4
n	10	10	10	10	10	10

Statistical significance when compared with control subjects
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

each sampling point the mean values of coronary patients were clearly higher than those of control subjects, the difference being very highly significant

The mean total cholesterol values, presented in Table 14 and Fig 10, were obtained by adding in each case the free cholesterol values to esterified cholesterol values

While in control subjects the four hour mean value was smaller than the fasting value, it was greater than the fasting value in all the test groups In males with diabetic heredity and in diabetics the four hour value exceeded that of the controls, the difference being significant In the coronary group all the mean values were greater than those of the controls and the difference was very highly significant

The 95 per cent confidence level four hours after the fat load 250 mg per

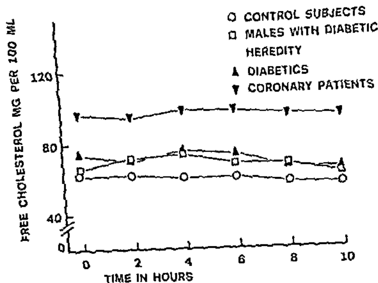


Fig. 9 Mean values of free serum cholesterol during the fat loading test in different groups

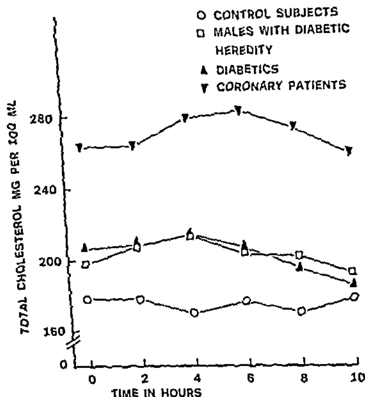


Fig. 10 Mean values of total serum cholesterol during the fat loading test in different groups.

TABLE 13 *Free serum cholesterol* (mg per 100 ml) in different groups during the fat loading test

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	62	62	60	60	57	56
Range	36—93	41—98	35—100	39—97	38—90	33—88
S D	±14	±16	±14	±15	±14	±16
S E M	± 3	± 3	± 3	± 3	± 3	± 4
n	22	22	22	22	22	13
Males with diabetic heredity						
Mean	66	71	74 *	68	67*	62
Range	40—97	45—123	44—108	40—85	45—89	34—87
S D	±18	±18	±18	±14	±12	±13
S E M	± 4	± 4	± 4	± 3	± 3	± 3
n	19	19	19	20	20	20
Diabetics						
Mean	74*	70	75*	73*	66*	64
Range	50—113	50—93	50—111	48—98	45—84	47—84
S D	±19	±16	±18	±15	±12	±13
S E M	± 6	± 6	± 6	± 4	± 4	± 4
n	11	8	10	11	10	9
Coronary patients						
Mean	97***	94***	98***	97***	95**	94 *
Range	68—127	62—139	78—122	69—119	69—112	74—120
S D	±21	±23	±14	±17	±14	±14
S E M	± 6	± 7	± 4	± 5	± 5	± 4
n	10	10	10	10	10	10

Statistical significance when compared with control subjects
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

each sampling point the mean values of coronary patients were clearly higher than those of control subjects, the difference being very highly significant

The mean total cholesterol values, presented in Table 14 and Fig 10, were obtained by adding in each case the free cholesterol values to esterified cholesterol values

While in control subjects the four hour mean value was smaller than the fasting value, it was greater than the fasting value in all the test groups In males with diabetic heredity and in diabetics the four hour value exceeded that of the controls, the difference being significant In the coronary group all the mean values were greater than those of the controls and the difference was very highly significant

The 95 per cent confidence level four hours after the fat load 250 mg per

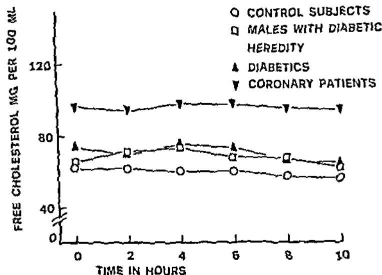


Fig. 9 Mean values of free serum cholesterol during the fat loading test in different groups.

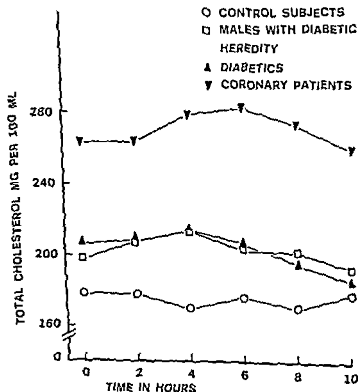


Fig. 10 Mean values of total serum cholesterol during the fat loading test in different groups.

TABLE 14 *Total serum cholesterol* (mg per 100 ml) *in different groups during the fat loading test*

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	178	175	170	176	170	175
Range	105—271	117—271	116—229	118—297	112—280	105—261
S D	±42	±38	±40	±44	±42	±44
S E M	± 9	± 8	±10	± 9	± 9	±12
n	21	22	22	22	22	13
Males with diabetic heredity						
Mean	199	208*	214***	203	201*	192
Range	170—288	138—261	145—269	140—271	150—257	134—274
S D	±45	±38	±39	±36	±41	±40
S E M	±10	± 8	± 9	± 8	± 9	± 9
n	19	19	19	20	20	20
Diabetics						
Mean	207	208	214*	206	194	185
Range	143—243	145—292	147—285	155—268	140—235	140—2[illegible]0
S D	±46	±50	±46	±32	±30	±28
S E M	±14	±20	±14	±10	±10	±10
n	11	9	10	10	10	9
Coronary patients						
Mean	264***	264***	279***	282***	272**	[illegible]**
Range	193—344	172—353	198—344	200—342	197—349	181—436
S D	±48	±58	±45	±44	±48	±53
S E M	±15	±18	±14	±14	±15	±16
n	10	10	10	10	10	10

Statistical significance when compared with control subjects
* $p < 0.05$ ** $p < 0.01$, *** $p < 0.001$

100 ml calculated from the mean value of controls, was exceeded by one control subject (5 per cent) by four males with diabetic heredity (20 per cent), by three diabetics (30 per cent), and by eight coronary patients (80 per cent)

Six hours after the fat load the values in males with diabetic heredity and diabetics were lower than four hours after the fat ingestion and this decreasing trend was still apparent eight and ten hours after the fat load Eight hours after the fat load the males with diabetic heredity showed a significantly higher mean value than did the controls ($p < 0.05$) The other differences were not significant

Non esterified fatty acids

The mean values obtained for the different groups during the fat loading test are given in Table 15 and Fig 11

TABLE 15 *Serum non esterified fatty acids (mEq per l) in different groups during the fat loading test*

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	0.301	0 390	0 426	0 359	0.3[illegible]6	0 295
Range	0 05—0 75	0 12—0 98	0 15—0 75	0 12—0 68	0 19—0.52	0 18—0 63
S D	±0 147	±0 185	±0 175	±0 155	±0 110	±0 116
S E M	±0 032	±0 040	±0 038	±0 034	±0 0[illegible]4	±0 031
n	21	21	21	21	21	14
Males with diabetic heredity						
Mean	0 322	0 417	0 540	0 519*	0 397	0 380
Range	0 12 —0 72	0 11—0 71	0 16—0 89	0.21—0 91	0 16—0 66	0 16—0 74
S D	±0 148	±0 156	±0 203	±0 245	±0 153	±0 152
S E M	±0 032	±0 034	±0 044	±0 05[illegible]	±0 033	±0 032
n	21	21	21	22	22	2[illegible]
Diabetics						
Mean	0 406	0 495	0 619	0 486	0 439	0.363
Range	0 19—0 83	0 23—1 50	0.28—1 43	0 14—0.80	0 12—0 77	0 08—0.59
S D	±0 177	±0 316	±0 326	±0 201	±0 204	±0 154
S E M	±0 049	±0 088	±0 094	±0 056	±0 059	±0 046
n	13	13	12	13	12	11
Coronary patients						
Mean	0.342	0.384	0 473	0 499	0 488*	0 477
Range	0 16—0 70	0 16—0 86	0 16—1 11	0 14—0 80	0 [illegible]0—1 08	0 17—0 95
S D	±0 146	±0 193	±0 243	±0 245	±0.255	±0.224
S E M	±0 030	±0 039	±0 048	±0 050	±0 071	±0 067
n	23	24	24	24	13	11

Statistical significance when compared with control subjects
$p < 0.05$ $p < 0.01$ $p < 0.001$

It was observed that the mean values of both males with diabetic heredity and diabetics were higher than in control subjects at each sampling point

The highest mean value two hours after the fat load was obtained in diabetics although there was no significant difference compared with the control subjects

Four hours after the fat load however the mean value of diabetics was significantly greater than in controls. The males with diabetic heredity also showed a somewhat but not significantly higher mean value than the control group

Compared with the controls the mean value for males with diabetic heredity was significantly higher six hours after fat administration and the mean values of diabetics and coronary patients were also higher

TABLE 14 *Total serum cholesterol (mg per 100 ml) in different groups during the fat loading test*

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	178	178	170	176	170	175
Range	105—271	117—271	116—229	118—297	112—280	105—[illegible]
S D	±42	±38	±40	±44	±42	±44
S E M	± 9	± 8	±10	± 9	± 9	±12
n	21	22	22	22	22	13
Males with diabetic heredity						
Mean	199	208*	214***	203	201*	192
Range	130—288	138—261	145—269	140—271	150—257	134—274
S D	±45	±38	±39	±36	±41	±40
S E M	±10	± 8	± 9	± 8	± 9	± 9
n	19	19	19	20	20	20
Diabetics						
Mean	207	208	214*	206	194	185
Range	143—243	145—292	147—285	155—268	140—235	140—220
S D	±46	±56	±46	±32	±30	±28
S E M	±14	±20	±14	±10	±10	±10
n	11	8	10	10	10	9
Coronary patients						
Mean	264***	264***	279***	282***	272***	[illegible]***
Range	193—344	172—353	198—344	200—342	197—349	181—336
S D	±49	±58	±45	±44	±48	±53
S E M	±15	±18	±14	±14	±15	±16
n	10	10	10	10	10	10

Statistical significance when compared with control subjects
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

100 ml, calculated from the mean value of controls, was exceeded by one control subject (5 per cent), by four males with diabetic heredity (20 per cent), by three diabetics (30 per cent), and by eight coronary patients (80 per cent)

Six hours after the fat load the values in males with diabetic heredity and diabetics were lower than four hours after the fat ingestion and this decreasing trend was still apparent eight and ten hours after the fat load Eight hours after the fat load the males with diabetic heredity showed a significantly higher mean value than did the controls ($p < 0.05$) The other differences were not significant

Non esterified fatty acids

The mean values obtained for the different groups during the fat loading test are given in Table 15 and Fig 11

TABLE 15 *Serum non esterified fatty acids* (mEq per l) in different groups during the fat loading test

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	0.301	0.390	0.426	0.389	0.3[illegible]6	0.295
Range	0.05—0.75	0.12—0.98	0.15—0.75	0.12—0.68	0.18—0.52	0.18—0.63
S.D	±0.147	±0.185	±0.175	±0.155	±0.110	±0.116
S.E.M	±0.032	±0.040	±0.038	±0.034	±0.024	±0.031
n	21	21	21	21	21	14
Males with diabetic heredity						
Mean	0.32[illegible]	0.417	0.540	0.519	0.397	0.380
Range	0.12—0.72	0.11—0.71	0.16—0.89	0.21—0.91	0.16—0.66	0.16—0.74
S.D	±0.148	±0.156	±0.203	±0.245	±0.153	±0.152
S.E.M	±0.032	±0.034	±0.044	±0.052	±0.033	±0.032
n	21	21	21	22	22	22
Diabetics						
Mean	0.406	0.495	0.619	0.486	0.439	0.[illegible]63
Range	0.19—0.83	0.23—1.50	0.28—1.43	0.14—0.80	0.12—0.77	0.08—0.59
S.D	±0.177	±0.316	±0.326	±0.201	±0.204	±0.154
S.E.M	±0.049	±0.088	±0.094	±0.056	±0.059	±0.046
n	13	13	12	13	12	11
Coronary patients						
Mean	0.342	0.384	0.4[illegible]3	0.499	0.488*	0.4[illegible]7
Range	0.16—0.70	0.16—0.86	0.16—1.11	0.14—0.80	0.20—1.08	0.17—0.95
S.D	±0.146	±0.193	±0.243	±0.245	±0.255	±0.224
S.E.M	±0.030	±0.039	±0.048	±0.050	±0.071	±0.067
n	23	24	24	24	13	11

Statistical significance when compared with control subjects
$p < 0.05$ $p < 0.01$ * $p < 0.001$

It was observed that the mean values of both males with diabetic heredity and diabetics were higher than in control subjects at each sampling point

The highest mean value two hours after the fat load was obtained in diabetics although there was no significant difference compared with the control subjects

Four hours after the fat load however the mean value of diabetics was significantly greater than in controls The males with diabetic heredity also showed a somewhat but not significantly higher mean value than the control group

Compared with the controls the mean value for males with diabetic heredity was significantly higher six hours after fat administration and the mean values of diabetics and coronary patients were also higher

Table 14 *Total serum cholesterol (mg per 100 ml) in different groups during the fat loading test*

	0 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs
Control subjects						
Mean	178	178	170	176	170	178
Range	105—271	117—271	116—229	118—297	112—280	105—261
S D	±42	±38	±40	±44	±42	±44
S E M	± 9	± 8	±10	± 9	± 9	±12
n	21	22	22	22	22	13
Males with diabetic heredity						
Mean	199	208*	214***	203	201*	192
Range	130—288	138—261	145—269	140—271	150—257	134—274
S D	±45	±38	±39	±36	±41	±40
S E M	±10	± 8	± 9	± 8	± 9	± 9
n	19	19	19	20	20	20
Diabetics						
Mean	207	208	214*	206	194	185
Range	143—243	145—292	147—285	155—268	140—235	140—2[illegible]0
S D	±46	±56	±46	±32	±30	±[illegible]5
S E M	±14	±20	±14	±10	±10	±10
n	11	8	10	10	10	9
Coronary patients						
Mean	264***	264***	279***	282***	272*	255**
Range	193—344	172—353	198—344	200—342	197—349	181—336
S D	±48	±58	±45	±44	±47	±[illegible]7
S E M	±15	±18	±14	±14	±15	±16
n	10	10	10	10	10	10

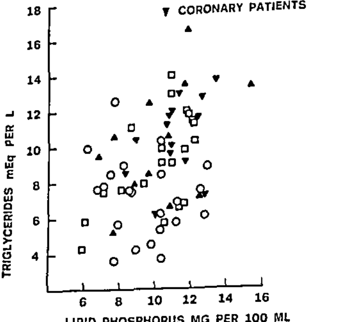
Statistical significance when compared with control subjects
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

100 ml, calculated from the mean value of controls, was exceeded by one control subject (5 per cent), by four males with diabetic heredity (20 per cent), by three diabetics (30 per cent), and by eight coronary patients (80 per cent)

Six hours after the fat load the values in males with diabetic heredity and diabetics were lower than four hours after the fat ingestion and this decreasing trend was still apparent eight and ten hours after the fat load Eight hours after the fat load the males with diabetic heredity showed a significantly higher mean value than did the controls ($p < 0.05$) The other differences were not significant

Non esterified fatty acids

The mean values obtained for the different groups during the fat loading test are given in Table 15 and Fig 11



F g 13 I lut o l p of s ru tr gl r l a l l p d p l p l us l ls f ur l urs af tl f t loal C r l t on o ff ts and t val s i d f f r t groups

Co trol subj cts	r —0 1	t 0 86	
M l s tl lal t o l d t	r — +0 68	t = 4 010	(1 < 0 0 1
I bet es	r +0 50	t = 1 850	
(ro nary p t ts	r +0 60	t	p < 0 05

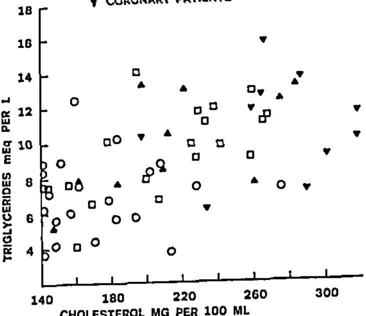


Fig 14 I l t o l l p of ru tr glyc r l l t l c ol st rol l ls f r l ours aft r t le fat loa l C rr lat on co ff c nts an l t valu s l f f r t groups

Co trol subj cts	r — +0 00	t 0 014
M l s l d l tl l r l y	r +0 41	t = 1 7
D al t s	r — +0 41	t = 1 8 0
(ro r p t ts	r — +0 7	t — 0 1 8

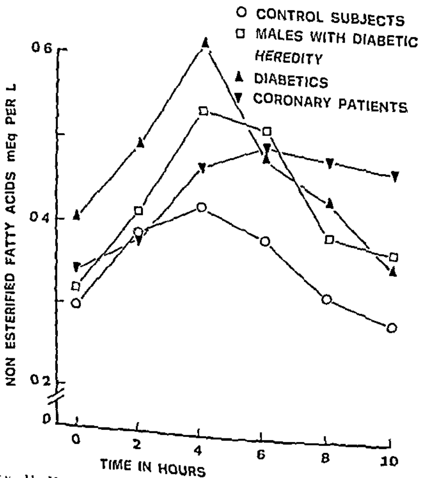


Fig. 11 Mean values of serum non esterified fatty acids during the fat loading test in different groups

Fig. 12 Absolute changes in serum non esterified fatty acids during the fat loading test in different groups

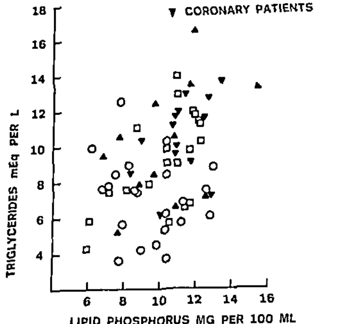


Fig. 13 [illegible] lationship of serum triglyceride [illegible] lipid phosphorus levels [illegible] Correlation coefficients and t values [illegible] groups

Control subjects	r = −0.1	t = 0.786	
Males with diabetic heredity	r = +0.68	t = 4.040	(p < 0.001)
Diabetics	r = +0.50	t = 1.850	
Coronary patients	r = +0.60	t = [illegible]65	(p < 0.05)

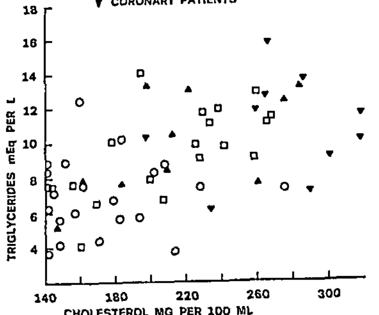


Fig. 14 [illegible] of serum triglyceride [illegible] total cholesterol levels [illegible] Correlation coefficients and t values [illegible] groups

Control subjects	r = +0.00	t = 0.014
Males with diabetic heredity	r = +0.41	t = [illegible]
Diabetics	r = +0.41	t = 1.9 0
Coronary patients	r = +0.27	t = 0. 98

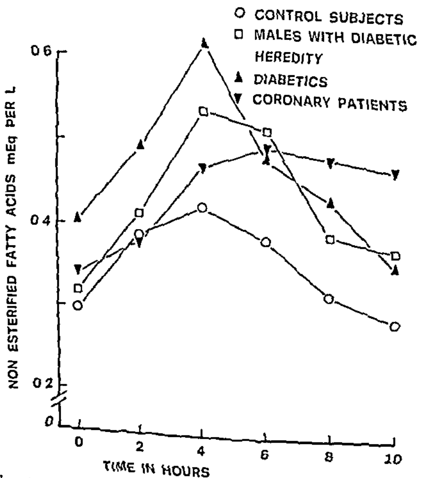


Fig. 11 [illegible]

Fig. 1[illegible] Absolute changes [illegible] esterified fatty acids [illegible]

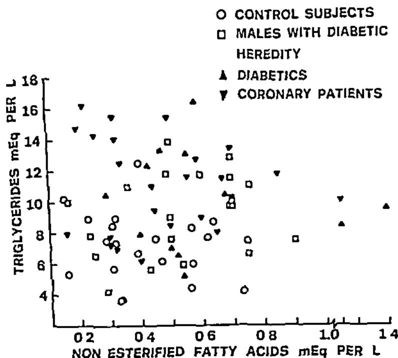


Fig 16 Relationship of serum triglyceride and non esterified fatty acids four hours after the fat load Correlation coefficients and t values in different groups

Control subjects	r = —0 15	t = 0 661
Males with diabetic heredity	r = +0 22	t = 0 975
Diabetics	r = —0 11	t = 0 343
Coronary patients	r = —0 11	t = 0 483

in Figs 13 14 15 and 16, and the r and t values are presented in the legends to the figures

In control subjects a significant correlation ($p < 0.01$) was found to be present between the serum lipid phosphorus and total cholesterol levels

In males with diabetic heredity a significant correlation was present between the triglyceride and lipid phosphorus values ($p < 0.001$) and also between the lipid phosphorus and total cholesterol values ($p < 0.05$)

The only significant correlation in diabetics was observed between the lipid phosphorus and total cholesterol levels ($p < 0.05$) although rather high r values were recorded also between the serum triglyceride and lipid phosphorus levels and serum triglyceride and cholesterol levels

In coronary patients the only significant correlation was present between *the serum triglyceride and lipid phosphorus levels* ($p < 0.05$)

No significant correlations were found to be present between the serum triglyceride and total cholesterol nor between the serum triglyceride and non esterified fatty acid levels.

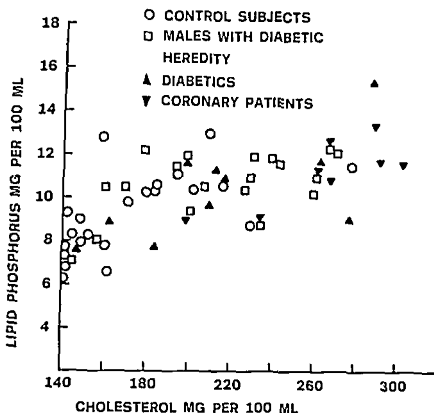


Fig 15 Relationship of serum lipid phosphorus and total cholesterol four hours after the fat load Correlation coefficients and t values in different groups

Control subjects	$r = +0.65$	$t = 3.774$	$(p < 0.01)$
Males with diabetic heredity	$r = +0.53$	$t = 2.550$	$(p < 0.05)$
Diabetics	$r = +0.72$	$t = 2.898$	$(p < 0.05)$
Coronary patients	$r = +0.64$	$t = 2.212$	

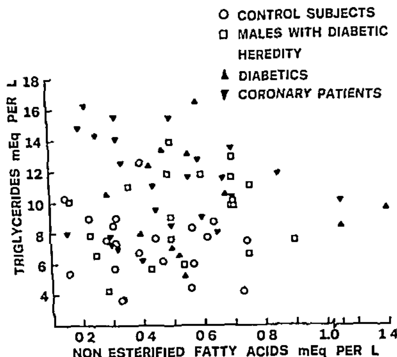
The mean values of coronary patients *eight and ten hours after the fat load* were significantly higher than those of the control subjects

Fig 12 illustrates the two hourly changes of non esterified fatty acids, taking the fasting level as zero value

It was found that of all the groups, the males with diabetic heredity showed the greatest rise both from fasting to two hour level and from two hour to four hour level, the latter change being significantly greater ($p < 0.05$) than in controls The rise from two-hour to four hour level was great in diabetics as well, although there was no significant difference *when compared with controls*

Interrelationships of serum triglyceride, lipid phosphorus, total cholesterol and non esterified fatty acid levels four hours after the fat load

Correlation coefficients were calculated for the triglyceride lipid phosphorus and total cholesterol values and for the triglyceride and non esterified fatty acid values four hours after the fat load The correlations are shown in scattergrams



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Control subjects	r = —0 15	t = 0 661
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Diabetics	r = —0 11	t = 0 343
Coronary patients	r = —0 11	t = 0 483

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In coronary patients the only significant correlation was present between the serum triglyceride and lipid phosphorus levels ($p < 0.05$)

No significant correlations were found to be present between the serum triglyceride and total cholesterol nor between the serum triglyceride and non esterified fatty acid levels.

Correlations between serum lipid values and glucose tolerance, conjunctival changes and body weight in males with diabetic heredity

Serum lipid values and glucose or cortisone glucose tolerance test

The correlations between the mean values of total lipids, triglycerides, total cholesterol and non esterified fatty acids in fasting state, four and eight hours after the fat load, on the one hand and the response to glucose or cortisone-glucose load, on the other hand, are shown in Table 16

The subjects were divided into three groups according to the results of glucose or cortisone glucose tolerance tests

TABLE 16 Serum lipids in fasting state, four and eight hours after the fat load in groups classified according to result of glucose or cortisone glucose tolerance test

	0 hrs			4 hrs			8 hrs		
	Gr I	Gr II	Gr III	Gr I	Gr II	Gr III	Gr I	Gr II	Gr III
Total lipids mg per 100 ml									
Mean	863	832	744	1083	1013	1048	890	870	812
S D	±203	±131	±179	±223	±230	±264	±161	±124	±192
S E M	± 90	± 54	± 57	±100	± 94	± 84	± 72	± 50	± 58
n	5	6	10	5	6	10	5	6	11
Triglycerides mEq per l									
Mean	5 6	6 1	4 8	9 9	9 9	8 8	5 9	6 7	5 1
S D	±2 21	±1 58	±1 66	±2 63	±1 68	±3 01	±2 63	±1 09	±1 70
S E M	±0 99	±0 65	±0 53	±1 18	±0 75	±0 95	±1 18	±0 44	±0 51
n	5	6	10	5	5	10	5	6	11
Total cholesterol mg per 100 ml									
Mean	239	201	181	240	211	209	218	215	187
S D	±42	±40	±42	±28	±40	±41	[illegible]	±55	±34
S E M	±21	±16	±14	±14	±16	±14	±12	±23	±11
n	4	6	9	4	6	9	4	6	10
Non esterified fatty acids mEq per l									
Mean	0 34	0 35	0 30	0 57	0 54	0 53	0 43	0 37	0 40
S D	±0 131	±0 212	±0 104	±0 162	±0 156	±0 229	±0 192	±0 116	±0 163
S E M	±0 059	±0 087	±0 033	±0 072	±0 064	±0 073	±0 086	±0 048	±0 049
n	5	6	10	5	6	10	5	6	11

Group I subjects with abnormal or borderline response to test
Group II subjects showing only glucosuria during the test
Group III subjects with normal response to test

Group I consisted of five subjects with abnormal or borderline response to glucose or cortisone glucose tolerance test Group II consisted of six subjects who exhibited glucosuria during the glucose or cortisone glucose tolerance test with normal blood glucose values Group III included the rest of the males with diabetic heredity, 11 subjects, having normal glucose or cortisone glucose tolerance tests

The subjects of Group I and Group II were found to have somewhat higher mean values of total lipids and triglycerides than those of Group III The mean level of total cholesterol was also

TABLE 17 Serum lipids in fasting state, four and eight hours after the fat load, in males with diabetic heredity with marked conjunctival changes as compared to those with few or no conjunctival changes.

	0 hrs		4 hrs		8 hrs	
	Marked changes	Few or no changes	Marked changes	Few or no changes	Marked changes	Few or no changes
Total lipids mg per 100 ml						
Mean	882	755	1186	976	993	799
S D	±185	±156	±223	±215	±120	±166
S E M	± 70	± 42	± 84	± 57	± 45	± 43
n	7	14	7	14	7	15
Triglycerides mEq per l						
Mean	5.7	5.2	9.8	8.8	5.9	5.6
S D	±1.32	±2.00	±3.11	±2.39	±1.63	±1.99
S E M	±0.50	±0.53	±1.1[illegible]	±0.66	±0.62	±0.51
n	7	14	[illegible]	13	7	15
Total cholesterol mg per 100 ml						
Mean	210	194	2[illegible]4	209	210	198
S D	±4[illegible]	±47	±43	±38	±32	±43
S E M	±17	±13	±1[illegible]	±11	±13	±12
n	6	13	6	13	6	14
Non esterified fatty acids mEq per l						
Mean	0.32	0.3	0.51	0.55	0.31	0.44
S D	±0.104	±0.168	±0.113	±0.238	±0.08[illegible]	±0.16[illegible]
S E M	±0.041	±0.045	±0.043	±0.064	±0.033	±0.042
n	[illegible]	14	[illegible]	14	[illegible]	15

$p < 0.05$ $p < 0.01$ $p < 0.001$

4

Correlations between serum lipid values and glucose tolerance, conjunctival changes and body weight in males with diabetic heredity

Serum lipid values and glucose or cortisone glucose tolerance test

The correlations between the mean values of total lipids, triglycerides, total cholesterol and non esterified fatty acids in fasting state four and eight hours after the fat load, on the one hand and the response to glucose or cortisone glucose load, on the other hand, are shown in Table 16

The subjects were divided into three groups according to the results of glucose or cortisone glucose tolerance tests

TABLE 16 Serum lipids in fasting state, four and eight hours after the fat load in groups classified according to result of glucose or cortisone glucose tolerance test

	0 hrs			4 hrs			8 hrs		
	Gr I	Gr II	Gr III	Gr I	Gr II	Gr III	Gr I	Gr II	Gr III
Total lipids mg per 100 ml									
Mean	863	832	744	1083	1013	1048	890	870	812
S D	±203	±131	±179	±223	±230	±264	±161	±124	±192
S E M	± 90	± 54	± 57	±100	± 94	± 84	± 72	± 50	± 58
n	5	6	10	5	6	10	5	6	11
Triglycerides mEq per l									
Mean	5.6	6.1	4.8	9.9	9.9	8.8	5.9	6.7	5.1
S D	±2.21	±1.58	±1.66	±2.63	±1.69	±3.01	±2.63	±1.09	±1.70
S E M	±0.99	±0.65	±0.53	±1.18	±0.75	±0.95	±1.18	±0.44	±0.51
n	5	6	10	5	5	10	5	6	11
Total cholesterol mg per 100 ml									
Mean	239	201	181	240	211	209	218	215	187
S D	±42	±40	±42	±28	±40	±41	±25	±55	±34
S E M	±21	±16	±14	±14	±16	±14	±12	±23	±11
n	4	6	9	4	6	9	4	6	10
Non esterified fatty acids mEq per l									
Mean	0.34	0.35	0.30	0.57	0.54	0.53	0.43	0.37	0.40
S D	±0.131	±0.212	±0.104	±0.162	±0.156	±0.229	±0.192	±0.116	±0.163
S E M	±0.059	±0.087	±0.033	±0.072	±0.064	±0.073	±0.086	±0.048	±0.049
n	5	6	10	5	6	10	5	6	11

Group I subjects with abnormal or borderline response to test
Group II subjects showing only glucosuria during the test
Group III subjects with normal response to test

TABLE 18 Serum lipids in fasting state, four and eight hours after the fat load, in overweight males with diabetic heredity as compared with normal or underweight group

	0 hrs		4 hrs		8 hrs	
	Over weight	Normal or under weight	Over weight	Normal or under weight	Over weight	Normal or under weight
Total lipids mg per 100 ml						
Mean	894*	725	1165	957	961**	763
S D	±123	±173	±105	±269	±95	±150
S E M	± 41	± 50	± 35	± 78	±32	± 43
n	9	12	9	12	9	13
Triglycerides mEq per l						
Mean	6.1	4.8	10.0	8.6	6.7*	5.0
S D	±1.91	±1.55	±2.21	±2.82	±1.87	±1.56
S E M	±0.63	±0.45	±0.78	±0.81	±0.62	±0.43
n	9	12	8	12	9	13
Total cholesterol mg per 100 ml						
Mean	251*	179	231	198	221	186
S D	±48	±33	±34	±39	±41	±35
S E M	±16	±11	±11	±12	±14	±11
n	9	10	9	10	9	11
Non esterified fatty acids mEq per l						
Mean	0.36	0.59	0.60	0.50	0.39	0.40
S D	±0.179	±0.119	±0.147	±0.233	±0.137	±0.168
S E M	±0.060	±0.034	±0.049	±0.067	±0.046	±0.047
n	9	12	9	12	9	12
Lipid phosphorus mg per 100 ml						
Mean	10.4	8.5	11.1	9.7	10.7	9.5
S D	±1.23	±2.25	±1.10	±2.33	±1.15	±2.45
S E M	±0.41	±0.65	±0.37	±0.67	±0.38	±0.68
n	9	12	9	12	9	13

$p < 0.05$ $p < 0.01$ $p < 0.001$

highest in Group I In all three sub groups of males with diabetic heredity, the fat loading curves were about similar as far as total lipids and triglycerides are concerned

Abnormally high total lipid levels (more than control mean +2 SD), occurred four or six hours after the fat load in three out of five subjects of Group I, in two out of five of Group II, and in three out of eleven of Group III

The non esterified fatty acid values in fasting state were slightly higher in Groups I and II than in Group III, but there was no significant difference

No clear differences were observed in mean values of serum lipid phosphorus between the three subgroups of males with diabetic heredity

Serum lipid values and conjunctival changes

In Table 17 are seen the total lipids, triglycerides, total cholesterol and non esterified fatty acid values of the seven subjects showing marked changes in the bulbar conjunctivae (in four or more of the aspects studied) as compared to those with few or no changes Here again, only the fasting values and the values obtained four and eight hours after the fat load are given

The mean values of total lipids, triglycerides and total cholesterol were somewhat higher, both in the fasting state and after the fat load, in subjects with marked conjunctival changes than in subjects showing few changes It might be of some significance that five of those eight males with diabetic heredity who had abnormally high total lipid values four hours after the fat lo were included in the group with mark conjunctival changes

The non esterified fatty acid valu did not differ in these two groups

The mean value of lipid phosphoru although not presented here, was slight higher in the group with marked co junctival changes

Serum lipid values and body weight

The effect of excess body weight o the fat loading test was studied by divid ing the males with diabetic heredity int two groups those with a body weigh exceeding the height minus 100 cm b 5 kg or more, and the rest of the sub jects The fasting mean values of tota lipids and lipid fractions and the mea values four and eight hours after the fa load are shown in Table 18

It was observed that the fasting total lipid values and also the various lipid fractions were higher in the 'over weight' group than in the 'normal or underweight' group The differences between the means of total lipids lipid phosphorus and total cholesterol were significant, whereas the mean values of triglycerides and non esterified fatty acids were not statistically different

The subjects belonging to the 'over weight' group showed after the fat load higher mean lipid values than did the subjects of the 'normal or underweight' group The differences relating to total lipids were statistically significant both four and eight hours after the fat load and relating to triglycerides eight hours after the fat load The differences be tween mean values of lipid phosphorus

TABLE 18 Serum lipids in fasting state, four and eight hours after the fat load in overweight males with diabetic heredity as compared with normal or underweight group

	0 hrs		4 hrs		8 hrs	
	Over weight	Normal or under weight	Over weight	Normal or under weight	Over weight	Normal or under weight
Total lipids mg per 100 ml						
Mean	894	725	1165*	957	961	763
S D	±123	±173	±105	±269	±95	±156
S E M	± 41	± 50	± 35	± 78	±32	± 43
n	9	12	9	12	9	13
Tri glycerides mEq per 1						
Mean	6.1	4.8	10.0	8.6	6.7*	5.0
S D	±1.91	±1.55	±2.21	±2.82	±1.87	±1.56
S E M	±0.63	±0.45	±0.78	±0.81	±0.62	±0.43
n	9	12	8	12	9	13
Total cholesterol mg per 100 ml						
Mean	221	179	231	198	221	186
S D	±48	±33	±34	±39	±41	±35
S E M	±16	±11	±11	±12	±14	±11
n	9	10	9	10	9	11
Non esterified fatty acids mEq per 1						
Mean	0.36	0.29	0.60	0.50	0.39	0.40
S D	±0.179	±0.119	±0.147	±0.233	±0.137	±0.168
S E M	±0.060	±0.034	±0.049	±0.067	±0.046	±0.047
n	9	12	9	12	9	12
Lipid phosphorus mg per 100 ml						
Mean	10.4	8.5	11.1	9.7	10.7	9.5
S D	±1.23	±2.25	±1.10	±2.33	±1.15	±1.45
S E M	±0.41	±0.65	±0.37	±0.67	±0.38	±0.68
n	9	12	9	12	9	13

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

highest in Group I In all three sub groups of males with diabetic heredity, the fat loading curves were about similar as far as total lipids and triglycerides are concerned

Abnormally high total lipid levels (more than control mean +2 SD), occurred four or six hours after the fat load in three out of five subjects of Group I, in two out of five of Group II, and in three out of eleven of Group III

The non esterified fatty acid values in fasting state were slightly higher in Groups I and II than in Group III, but there was no significant difference

No clear differences were observed in mean values of serum lipid phosphorus between the three subgroups of males with diabetic heredity

Serum lipid values and conjunctival changes

In Table 17 are seen the total lipids, triglycerides, total cholesterol and non esterified fatty acid values of the seven subjects showing marked changes in the bulbar conjunctivae (in four or more of the aspects studied) as compared to those with few or no changes Here again, only the fasting values, and the values obtained four and eight hours after the fat load are given

The mean values of total lipids, triglycerides and total cholesterol were somewhat higher, both in the fasting state and after the fat load, in subjects with marked conjunctival changes than in subjects showing few changes It might be of some significance that five of those eight males with diabetic heredity who had abnormally high total lipid values four hours after the fat load were *included* in the group with marked conjunctival changes

The non esterified fatty acid values did not differ in these two groups

The mean value of lipid phosphorus, although not presented here, was slightly higher in the group with marked conjunctival changes

Serum lipid values and body weight

The effect of excess body weight on the fat loading test was studied by dividing the males with diabetic heredity into two groups those with a body weight exceeding the height minus 100 cm by 5 kg or more, and the rest of the subjects The fasting mean values of total lipids and lipid fractions and the mean values four and eight hours after the fat load are shown in Table 18

It was observed that the fasting total lipid values and also the various lipid fractions were higher in the "over weight" group than in the "normal or underweight" group The differences between the means of total lipids lipid phosphorus and total cholesterol were significant, whereas the mean values of triglycerides and non esterified fatty acids were not statistically different

The subjects belonging to the "over weight" group showed, after the fat load higher mean lipid values than did the subjects of the "normal or underweight" group The differences relating to total lipids were statistically significant both four and eight hours after the fat load and relating to triglycerides eight hours after the fat load The differences between mean values of lipid phosphorus

TABLE 18 Serum lipids in fasting state, four and eight hours after the fat load in overweight males with diabetic heredity as compared with normal or underweight group

	0 hrs		4 hrs		8 hrs	
	Overweight	Normal or underweight	Overweight	Normal or underweight	Overweight	Normal or underweight
Total lipids mg per 100 ml						
Mean	894	[illegible]	1165	95	961**	63
S D	±1?3	±1 3	±10	±269	±95	±156
S E M	± 41	± 50	± 35	± 8	±37	± 43
n	9	1?	9	1?	9	13
Triglycerides mEq per l						
Mean	6 1	4.8	10 0	8 6	6 *	5 0
S D	±1 91	±1 55	±2 ?1	±2 8?	±1 8	±1.56
S E M	±0 63	±0 45	±0 8	±0 81	±0 6?	±0 43
n	9	1	8	1?	9	13
Total cholesterol mg per 100 ml						
Mean	? 1	1 9	?31	198	?1	186
S D	±48	±33	±34	±39	±41	±35
S E M	±16	±11	±11	±1	±14	±11
n	9	10	9	10	9	11
Non esterified fatty acids mEq per l						
Mean	0 36	0 ?9	0 60	0 50	0 39	0 40
S D	±0 1 9	±0 119	±0 14	±0 ?33	±0 137	±0 168
S E M	±0 060	±0 034	±0 049	±0 06	±0 046	±0 04
n	9	1?	9	1?	9	12
Lipid phosphorus mg per 100 ml						
Mean	10 4	8 5	11 1	9	10 7	9.5
S D	±1 ?3	± ?5	±1 10	±2.33	±1 15	± 45
S E M	± 41	±0 65	±0 3	±0 67	±0 38	±0 68
n	9	1	9	1	9	13

$p < 0.05$ $p < 0.01$ $p < 0.001$

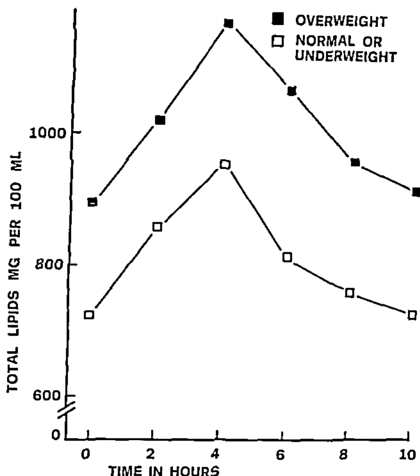

Fig 17 Changes in serum total lipids during the fat loading test in males with diabetic heredity grouped according to body weight

total cholesterol and non esterified fatty acids were not significant

Fig 17 illustrates the changes in total lipids in the two groups during the fat loading test Although the mean fasting value of the "overweight" group was significantly higher than that of the rest of the subjects the curves are entirely similar in shape

Fasting serum lipid values

The fasting values of serum optical density did not permit a differentiation between the clinical groups and the control subjects. The values may be within normal range in spite of abnormal serum lipid pattern and abnormal response to a fat load.

The determination of total lipids from the fasting serum showed that both the diabetics and the coronary patients had significantly higher mean values than the control subjects. The mean value of males with diabetic heredity was also somewhat higher than that of control subjects. Individual variations however were great in all the groups and normal total lipid values were often seen in coronary patients also.

The triglyceride values were in general higher than those earlier reported for instance by SVANBORG and SVENNERHOLM (1961), NIKKILÄ and KONTTINEN (1962), HOLLISTER (1963) and JAKOBSON *et al* (1965). The control group included six subjects with unexpectedly high fasting triglyceride values exceeding 7.0 mEq per l. Three of these subjects also had high cholesterol values while three others har low serum cholesterol values. There was no reason to exclude these subjects from the control material. The fairly high mean fasting value of triglycerides in this group is explained by his fact. Males with diabetic heredity also included a few subjects with high fasting values. — The rather high triglyceride values are also accounted for in part by the method here used involving determination of ester linkages. The triglyceride fraction included also the diglycerides of serum, which represent 5 to 10 per cent of the total amount of glycerolesters.

Only in the case of coronary patients were the mean lipid phosphorus values significantly higher than in the control group, but a tendency towards elevated values appeared also in males with diabetic heredity and diabetics. This further strengthened the evidence that the lipid metabolism deviates from the normal in many subjects with diabetic heredity.

The free and esterified cholesterol values obtained by the silica gel chromatography method were lower than those obtained by direct estimation from blood serum using for example the p-sulphonic acid reaction. A similar finding has also been presented by SVANBORG and SVENNERHOLM (1961). The fasting values for control subjects however were in the same range as those reported by NIKKILÄ and KONTTINEN (1962) in a group of healthy Finnish servicemen of similar age distribution.

Coronary patients showed a much higher mean serum cholesterol value

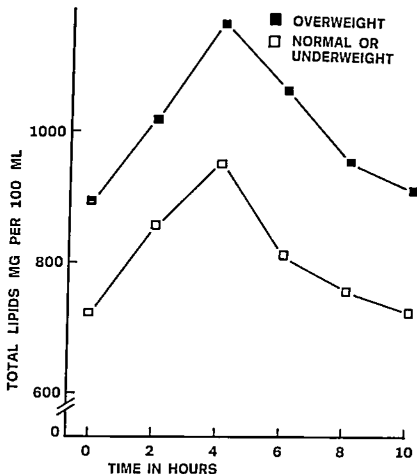

Fig 17 Changes in serum total lipids during the fat loading test in males with diabetic heredity grouped according to body weight

total cholesterol and non esterified fatty acids were not significant

Fig 17 illustrates the changes in total lipids in the two groups during the fat loading test Although the mean fasting value of the 'overweight' group was significantly higher than that of the rest of the subjects the curves are entirely similar in shape

as late as eight hours after the fat load. The same trend towards delayed normalization of lipid levels in these two groups was observed also in total lipids. In diabetics too the duration of lipemia was longer than in control subjects, although this was less marked than in the above groups.

The changes in serum optical density after the fat load were directly related to changes in total lipids and triglycerides in all groups. This observation has been made by many previous investigators (BARRIT 1956, OSMON et al. 1957, BROWN et al. 1961, STUTMAN et al. 1961, HOLLISTER 1963, ANGERVALL 1964). Because measurement of serum optical density is easy, it can be used for rough estimation of the response to an orally administered fat load. The determination should be done four or six hours after fat ingestion.

The changes in lipid phosphorus after a fat load were remarkably similar in all the four groups, although a tendency to delayed normalization was observed in males with diabetic heredity and coronary patients. Contrary to what was the case with the triglycerides, the mean lipid phosphorus levels were elevated in all groups as late as ten hours after the fat load. When the four hour lipid phosphorus levels were correlated to the four hour triglyceride levels, a significant correlation was found to be present both in males with diabetic heredity ($p < 0.001$) and in coronary patients ($p < 0.01$), while the control subjects showed no correlation ($r = -0.17$). In atherosclerotic patients POMERANZE et al. 1954) and ANGERVALL (1964) have earlier shown a similar correlation between great alimentary lipemia and high phospholipid increase.

The changes in both free and total cholesterol after fat ingestion were small. It was observed, however, that the majority of control subjects showed a decrease in total cholesterol level four hours after the fat load. This resulted in decrease of mean total cholesterol concentration at this sampling point. A similar observation has been made earlier by NIKKILÄ and KONTTINEN (1962) and ANGERVALL (1964), while HAMMERL et al. (1962) have demonstrated an increase of the fasting cholesterol value after a fatty meal. As contrasted with control subjects, males with diabetic heredity, diabetics and coronary patients showed increased mean levels of total cholesterol after the fat load. Although the increase was not significant, this finding does suggest that the response to a fat load in clinically healthy males with diabetic heredity differs from that of normal males and parallels that observed in diabetics and coronary patients.

The four hour cholesterol levels were also found to be related to the four hour triglyceride levels in males with diabetic heredity and diabetics ($r = 0.41$), although the correlation was not significant. In control subjects no correlation was present between these values ($r = 0.00$). The four hour cholesterol levels were, however, in significant correlation to the four hour lipid phosphorus levels in both control subjects and males with diabetic heredity and diabetics.

A rise of non-esterified fatty acid concentration was already noted two hours after the fat load in most cases. This

than the control group (difference very highly significant) This was to be expected on the basis of earlier investigations and this finding confirms the value of cholesterol determination as a screening test for deranged lipid metabolism in coronary patients The *mean* values for diabetics and males with diabetic heredity were somewhat higher than that of control subjects, but there was no statistical difference — The ratio of free cholesterol to esterified cholesterol was about 1 2 in all groups, which accords well with the figures given by various authors

The mean value of non esterified fatty acids in the fasting serum was somewhat higher in males with diabetic heredity and especially in diabetics than it was in the control group It has been stated earlier that the non esterified fatty acid values are often elevated in prediabetics (CATELLIER *et al* 1964, JAKOBSON *et al* 1965, PFEIFFER 1965) The fact that the mean level of non esterified fatty acids was not significantly elevated in the present material consisting of males with diabetic heredity may be attributed to the circumstance that it included subjects who were not "true prediabetics" as defined for instance by CAMERINI DAVALOS (1965) — Even in diabetics the elevation of non esterified fatty acid concentration was not significant This was evidently due to the mild diabetes of the patients here studied

Serum lipid changes after the fat load

The standard fat load, 200 ml of heavy cream caused a significant rise in serum optical density and in all the lipid components examined except cholesterol, which showed inconsistent changes

In the control group the mean levels of total lipids and triglycerides were about the same two hours and four hours after cream ingestion The peak level was evidently reached in most cases during the interval from two to four hours after the fat load This coincides well with the results of HIRSCH and CARBONARO (1950), OSMON *et al* (1957), BROWN *et al* (1961) and STUTMAN *et al* (1961), whereas, in the series presented by NIKKILÄ and KONTTINEN (1962), BROWN *et al* (1963), DENBOROUGH (1963), HOLLISTER (1963), SHAH *et al* (1963) and ANGERVALL (1964), the peak level of serum triglycerides or total esterified fatty acids occurred four or five hours after fat ingestion

The changes of total lipid and triglyceride levels two hours after the fat load were not significantly different in the four groups studied As regards the change from two to four hour level however, the three test groups differed from the control group Males with diabetic heredity and coronary patients showed a marked rise in total lipids and triglycerides The change was much greater than in the control group (difference very highly significant) The change in total lipids in diabetics was smaller, but still significantly greater than in the controls

Six hours after the fat load the mean level of triglycerides had returned in control subjects to the fasting level In coronary patients and also in males with diabetic heredity the mean triglyceride levels were higher than the fasting levels

as late as eight hours after the fat load The same trend towards delayed normalization of lipid levels in these two groups was observed also in total lipids. In diabetics too, the duration of lipemia was longer than in control subjects although this was less marked than in the above groups

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(1964) similarly found that hyper cholesterolemia was more common in subjects with positive or borderline glucose tolerance test — In the present study, the lipid values of the subjects with normal response to the glucose or cortisone glucose tolerance test were about the same as in the control group This corresponds well with the results presented by CAMERINI DAVALOS *et al* (1965), who found no difference in the levels of serum cholesterol and triglycerides between the groups of normal subjects and close relatives of diabetics with normal glucose tolerance

The response to fat loading was very similar in males with diabetic heredity irrespective of the result of glucose or cortisone glucose tolerance test and deviated clearly from the response to fat loading obtained in control subjects *This finding* indicates that hyperlipemia after a fat load might be another feature characteristic of close relatives of diabetics

The conjunctival changes seemed likewise to be related to the serum lipid values *Both the fasting levels and the* levels after fat loading were somewhat higher in males with diabetic heredity with marked conjunctival changes than in those with few or no changes. The shape of the fat loading curve was almost similar in both these groups and differed from that of control subjects The total lipids were significantly higher both four and eight hours *after* the fat ingestion in subjects with marked changes than in those with few changes This finding may bear a correlation to the increased proneness of these subjects to subsequent atherosclerotic changes A follow up study is needed to clarify this question

Obese males with diabetic heredity had *significantly* higher mean fasting values of total lipids, lipid phosphorus and total cholesterol than had the normal or *underweight group The response* to fat loading was very similar in the two groups and in both of them the changes in *total lipids after* a fat load differed significantly from those of control subjects Thus the difference between males with diabetic heredity and control subjects observed after fat loading could not be explained by the higher mean weight of the former — *Obesity* is regarded as a sign indicative of prediabetic state and this may indeed have been the cause of the high *fasting* lipid values of the obese group

The finding of almost similar fat loading curves in obese and in normal or underweight subjects coincides well with the results of OPPENHEIM and BRUGER 1943 BARRIT *1956* and ANGERVALL *1964* It also rules out the possibility that the postprandial hyperlipemia in males with *diabetic heredity was connected only* with the increased fasting lipid levels of obese subjects. Postalimentary hyperlipemia in normal *subjects and in* coronary patients has been ascribed to the above mechanism by DENBOROUGH (1963) ANGERVALL (1964) *etc*

The significance of serum lipid changes after the fat load

The significance of serum lipid determinations after fat loading has been *a* matter of controversy It has been demonstrated that high total lipid and tri

finding contrasts with the results of Munkner (1959 a), Sullivan (1962), Shah *et al* (1963) and Hollister (1963), who all observed a decrease at this point On the other hand, Castelli *et al* (1966) found a clear rise of non-esterified fatty acid values three hours after fat ingestion in all subjects studied This corresponds well with the findings in the present study No explanation can be offered for the differing observations — The peak level of non-esterified fatty acids was reached in most cases four hours after fat ingestion The rise from the two to four hour level was greatest in males with diabetic heredity and was significantly greater than that shown by control subjects A close parallelism with the response of diabetics was also observed This finding may reflect a delayed esterification of non esterified fatty acids in the adipose tissue due to lack of α glycerophosphate This mechanism is held responsible for increased circulating non esterified fatty acids in diabetics (Jeanrenaud 1961) Differences in the rate of absorption, transfer from blood, and hydrolysis of triglyceride may exist The fact is, however that close relatives of diabetics after fat loading showed a trend towards increased non esterified fatty acid levels similar to those of diabetics — No significant correlation existed between the non esterified fatty acid and triglyceride levels four hours after the fat load in any of the four groups

Waldron and Nichols (1952) and Fullerton *et al* (1953) among other investigators, have shown that lipemia accelerates blood coagulation An inhibitory mechanism to fibrinolysis induced by lipemia has been demonstrated by Greig (1956) and a decrease in tissue oxygen tension during lipemia by Joyner *et al* (1960) In males with diabetic heredity, the postalimentary hyperlipemia, although of short duration, might thus be a contributing factor in the development of atherosclerotic and thrombotic manifestations at a relatively young age As already stated, recurrent post alimentary hyperlipemia has been assumed to be responsible for atherosclerotic manifestations in general (*e g* Moreton 1950)

Correlations between serum lipid values and glucose tolerance, conjunctival changes and body weight in males with diabetic heredity

When the close relatives of diabetics were grouped according to the result of glucose or cortisone glucose tolerance test, it was found that the subjects with an abnormal or borderline response showed somewhat higher fasting lipid values than those with a normal response Especially the serum cholesterol values were elevated The subjects presenting glucosuria during the test with normal blood glucose values also had somewhat higher lipid values than did those with normal response This finding agrees well with the investigation of Jakobson *et al* (1965) who observed that the mean values of serum triglycerides were somewhat although not significantly higher in subjects with a positive response to prednisone glucose tolerance test than in subjects with less impairment of glucose tolerance Chazan *et al*

(1964) similarly found that hyper cholesterolemia was more common in subjects with positive or borderline glucose tolerance test — In the present study, the lipid values of the subjects with normal response to the glucose or cortisone glucose tolerance test were about the same as in the control group This corresponds well with the results presented by CAMERINI DÁVALOS et al (1965), who found no difference in the levels of serum cholesterol and triglycerides between the groups of normal subjects and close relatives of diabetics with normal glucose tolerance

The response to fat loading was very similar in males with diabetic heredity irrespective of the result of glucose or cortisone glucose tolerance test and deviated clearly from the response to fat loading obtained in control subjects This finding indicates that hyperlipemia after a fat load might be another feature characteristic of close relatives of diabetics

The conjunctival changes seemed likewise to be related to the serum lipid values. Both the fasting levels and the levels after fat loading were somewhat higher in males with diabetic heredity with marked conjunctival changes than in those with few or no changes The shape of the fat loading curve was almost similar in both these groups and differed from that of control subjects The total lipids were significantly higher both four and eight hours after the fat ingestion in subjects with marked changes than in those with few changes. This finding may bear a correlation to the increased proneness of these subjects to subsequent atherosclerotic changes A follow up study is needed to clarify this question

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finding contrasts with the results of MUNKNER (1959 a), SULLIVAN (1962), SHAH *et al* (1963) and HOLLISTER (1963), who all observed a decrease at this point. On the other hand, CASTELLI *et al* (1966) found a clear rise of non esterified fatty acid values three hours after fat ingestion in all subjects studied. This corresponds well with the findings in the present study. No explanation can be offered for the differing observations. — The peak level of non esterified fatty acids was reached in most cases four hours after fat ingestion. The rise from the two to four hour level was greatest in males with diabetic heredity and was significantly greater than that shown by control subjects. A close parallelism with the response of diabetics was also observed. This finding may reflect a delayed esterification of non esterified fatty acids in the adipose tissue due to lack of α glycerophosphate. This mechanism is held responsible for increased circulating non esterified fatty acids in diabetics (JEANRENAUD 1961). Differences in the rate of absorption, transfer from blood, and hydrolysis of triglyceride may exist. The fact is, however, that close relatives of diabetics after fat loading showed a trend towards increased non esterified fatty acid levels similar to those of diabetics. — No significant correlation existed between the non esterified fatty acid and triglyceride levels four hours after the fat load in any of the four groups.

WALDRON and NICHOLS (1952) and FULLERTON *et al* (1953) among other investigators have shown that lipemia accelerates blood coagulation. An inhibitory mechanism to fibrinolysis induced by lipemia has been demonstrated by GREIG (1956) and a decrease in tissue oxygen tension during lipemia by JOYNER *et al* (1960). In males with diabetic heredity, the postalimentary hyperlipemia, although of short duration, might thus be a contributing factor in the development of atherosclerotic and thrombotic manifestations at a relatively young age. As already stated, recurrent postalimentary hyperlipemia has been assumed to be responsible for atherosclerotic manifestations in general (*e g* MORETON 1950).

Correlations between serum lipid values and glucose tolerance, conjunctival changes and body weight in males with diabetic heredity

When the close relatives of diabetics were grouped according to the result of glucose or cortisone glucose tolerance test, it was found that the subjects with an abnormal or borderline response showed somewhat higher fasting lipid values than those with a normal response. Especially the serum cholesterol values were elevated. The subjects presenting glucosuria during the test with normal blood glucose values also had somewhat higher lipid values than did those with normal response. This finding agrees well with the investigation of JAKOBSON *et al* (1965) who observed that the mean values of serum triglycerides were somewhat although not significantly higher in subjects with a positive response to prednisone glucose tolerance test than in subjects with less impairment of glucose tolerance. CHAZAN *et al*

(1964) similarly found that hyper cholesterolemia was more common in subjects with positive or borderline glucose tolerance test — In the present study the lipid values of the subjects with normal response to the glucose or cortisone glucose tolerance test were about the same as in the control group This corresponds well with the results presented by CAMERINI DAVALOS *et al* (1965) who found no difference in the levels of serum cholesterol and triglycerides between the groups of normal subjects and close relatives of diabetics with normal glucose tolerance.

The response to fat loading was very similar in males with diabetic heredity irrespective of the result of glucose or cortisone glucose tolerance test and deviated clearly from the response to fat loading obtained in control subjects This finding indicates that hyperlipemia after a fat load might be another feature characteristic of close relatives of diabetics

The conjunctival changes seemed likewise to be related to the serum lipid values Both the fasting levels and the levels after fat loading were somewhat higher in males with diabetic heredity with marked conjunctival changes than in those with few or no changes The shape of the fat loading curve was almost similar in both these groups and differed from that of control subjects The total lipids were significantly higher both four and eight hours after the fat ingestion in subjects with marked changes than in those with few changes This finding may bear a correlation to the increased proneness of these subjects to subsequent atherosclerotic changes A follow up study is needed to clarify this question

Obese males with diabetic heredity had significantly higher mean fasting values of total lipids, lipid phosphorus and total cholesterol than had the normal or underweight group The response to fat loading was very similar in the two groups, and in both of them the changes in total lipids after a fat load differed significantly from those of control subjects Thus the difference between males with diabetic heredity and control subjects observed after fat loading could not be explained by the higher mean weight of the former — Obesity is regarded as a sign indicative of prediabetic state and this may indeed have been the cause of the high fasting lipid values of the obese group

The finding of almost similar fat loading curves in obese and in normal or underweight subjects coincides well with the results of OPPENHEIM and BRUGER 1943 BARRIT 1956 and ANGERVALL 1964 It also rules out the possibility that the postprandial hyperlipemia in males with diabetic heredity was connected only with the increased fasting lipid levels of obese subjects Postalimentary hyperlipemia in normal subjects and in coronary patients has been ascribed to the above mechanism by DENBOROUGH (1963) ANGERVALL (1964) etc

The significance of serum lipid changes after the fat load

The significance of serum lipid determinations after fat loading has been a matter of controversy It has been demonstrated that high total lipid and tri

finding contrasts with the results of MUNKNER (1959 a), SULLIVAN (1962), SHAH *et al* (1963) and HOLLISTER (1963), who all observed a decrease at this point. On the other hand, CASTELLI *et al* (1966) found a clear rise of non-esterified fatty acid values three hours after fat ingestion in all subjects studied. This corresponds well with the findings in the present study. No explanation can be offered for the differing observations. — The peak level of non-esterified fatty acids was reached in most cases four hours after fat ingestion. The rise from the two to four hour level was greatest in males with diabetic heredity and was significantly greater than that shown by control subjects. A close parallelism with the response of diabetics was also observed. This finding may reflect a delayed esterification of non-esterified fatty acids in the adipose tissue due to lack of α-glycerophosphate. This mechanism is held responsible for increased circulating non-esterified fatty acids in diabetics (JEANRENAUD 1961). Differences in the rate of absorption, transfer from blood, and hydrolysis of triglyceride may exist. The fact is, however, that close relatives of diabetics after fat loading showed a trend towards increased non-esterified fatty acid levels similar to those of diabetics. — No significant correlation existed between the non-esterified fatty acid and triglyceride levels four hours after the fat load in any of the four groups.

WALDRON and NICHOLS (1952) and FULLERTON *et al* (1953), among other investigators, have shown that lipemia accelerates blood coagulation. An inhibitory mechanism to fibrinolysis induced by lipemia has been demonstrated by GREIG (1956) and a decrease in tissue oxygen tension during lipemia by JOYNER *et al* (1960). In males with diabetic heredity, the postalimentary hyperlipemia, although of short duration, might thus be a contributing factor in the development of atherosclerotic and thrombotic manifestations at a relatively young age. As already stated, recurrent postalimentary hyperlipemia has been assumed to be responsible for atherosclerotic manifestations in general (*e g* MORETON 1950).

Correlations between serum lipid values and glucose tolerance, conjunctival changes and body weight in males with diabetic heredity

When the close relatives of diabetics were grouped according to the result of glucose or cortisone glucose tolerance test, it was found that the subjects with an abnormal or borderline response showed somewhat higher fasting lipid values than those with a normal response. Especially the serum cholesterol values were elevated. The subjects presenting glucosuria during the test with normal blood glucose values also had somewhat higher lipid values than did those with normal response. This finding agrees well with the investigation of JAKOBSON *et al* (1965) who observed that the mean values of serum triglycerides were somewhat although not significantly higher in subjects with a positive response to prednisone glucose tolerance test than in subjects with less impairment of glucose tolerance. CHAZAN *et al*

SUMMARY

The aim of this investigation was to study a group of close relatives of diabetics with respect to their response to an orally administered fat load.

The material consisted of a total of 82 males including 22 sons of diabetic patients, 22 control subjects with corresponding age distribution, 13 recently diagnosed mild diabetics and 25 coronary patients.

A fat loading test (200 ml of standard heavy cream) was performed on all subjects and the blood samples were collected at two hourly intervals during ten hours.

The serum optical density was measured at 620 mμ. The total lipids were determined using chloroform methanol extraction and purification method. The non esterified fatty acids were determined by a modified sublimation method and the lipids were then fractionated into triglycerides, free cholesterol and esterified cholesterol. Lipid phosphorus was determined separately from each sample.

Males with diabetic heredity were subjected to glucose and cortisone glucose tolerance tests and the conjunctival vessels were examined with a slit lamp at a magnification of ×66.

1. The fasting serum values of total lipids, lipid phosphorus and both free and total cholesterol were in males with diabetic heredity somewhat higher than in the controls although no statistically significant differences were found.

In recently diagnosed diabetics and in coronary patients the mean fasting values of total lipids, triglycerides and free cholesterol were significantly higher than in the controls, and the same applies to the mean levels of lipid phosphorus and total cholesterol of coronary patients.

2. In the case of males with diabetic heredity the response to fat load differed from that of controls though marked overlapping of individual values occurred. The mean values of serum optical density, total lipids, triglycerides and free and total cholesterol were significantly greater four hours after the fat load than were the corresponding values of control subjects. Six hours after the fat load the mean values of lipid phosphorus and non esterified fatty acids were significantly higher in males with diabetic heredity than in control subjects. The mean total lipid values showed a significantly higher level as late as ten hours after the fat load.

The two-hourly changes of the various lipid fractions in males with diabetic heredity were remarkably similar to those found in diabetics and coronary patients.

3. Two males with diabetic heredity

glyceride values four or seven hours after a fat load are connected with elevated fasting values (DENBOROUGH 1963, ANGERVALL 1964). In the present investigation, no such correlation could be shown in males with diabetic heredity, when the relationship between the fasting triglyceride levels and the maximal increase in triglyceride content recorded two, four or six hours after the fat load was calculated. A trend to a positive correlation was, however, found in the coronary patients. If the correlation was calculated between the fasting triglyceride levels and the increase observed four hours after the fat load as in the study of ANGERVALL (1964), the r and t values were clearly higher. In this respect the results of the present investigation were not in disagreement with those presented earlier.

However, BERKOWITZ (1960, 1965), in particular, stresses the importance of fat loading in discovering subjects with abnormal lipid metabolism. In the present series, the 95 per cent confidence limit (calculated from the control material) of total lipids in fasting state was exceeded by two out of 21 males with diabetic heredity and by seven out of 24 coronary patients. The corresponding limit four hours after the fat load was exceeded by eight males with diabetic heredity and by 15 coronary patients. For triglycerides these figures were, respectively, one and four in fasting state and five and 13 four hours after the fat load. The figures were almost similar in diabetics. This shows that a fat loading test reveals abnormalities in lipid metabolism in subjects with normal or only moderately elevated fasting lipid values.

Measurement of serum optical density four hours after the fat load was almost as good an index of a probably abnormal reaction to fat load as was estimation of total lipids or triglycerides. Thus it can be used as a simple method in examining the individual response to fat loading.

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3 Two males with diabetic heredity

showed an abnormal response to the cortisone glucose tolerance test, and three others showed a borderline response to either the glucose tolerance or cortisone-glucose tolerance test (Group I) Six subjects exhibited glucosuria with normal blood glucose values during the glucose or cortisone glucose tolerance test (Group II) Comparison of the mean fasting serum lipid values of these subjects to those of subjects with normal glucose or cortisone glucose tolerance test (Group III) indicated that the first two groups presented somewhat higher values Yet the shape of the fat loading curve was almost similar in all the three subgroups

The conjunctival vascular bed showed many changes in males with diabetic heredity The most common change was increased arteriole venule ratio (16 subjects), followed by venular saccular micropools (14 subjects), tortuosity of small blood vessels (10 subjects), intravascular erythrocyte aggregation (8 subjects) and capillary aneurysms (5 subjects) Seven subjects displayed definite changes in four or more of the different aspects studied, all of them showed intravascular erythrocyte aggregation — In these last seven subjects, the mean values of serum total lipids and different lipid fractions were somewhat higher, both in fasting state and after fat loading, than in the rest of the group These groups did not differ as regards non esterified fatty acid levels

The fasting mean values of serum lipids in obese males with diabetic heredity were clearly higher than the corresponding values of normal or underweight males with diabetic heredity The fat loading curves, however, were almost similar in shape in both groups and differed from that of the control group

4 The fat loading test was found to be valuable especially in studying subjects with normal or only slightly elevated fasting lipid values In males with diabetic heredity, and also in many diabetics and coronary patients who presented slightly elevated fasting serum lipid values, the determination of total lipids, triglycerides or serum optical density after the fat load often disclosed a clearly abnormal pattern In most cases the fat loading curve deviated most clearly from that of the controls four or six hours after fat ingestion For practical purposes it thus seems to suffice to determine the total lipids or triglycerides four hours after the fat load Measurement of serum optical density, four hours after the fat load can be used as a rough index of the individual response to such loading

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Turku, December 1966

Veikko Kallio

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BY

RUNE SANNERSTEDT

Accompanies Vol. 180

GÖTEBORG 1966

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FROM THE DEPARTMENT OF MEDICINE I (PROFESSOR L WERKO), SAHLGRENSKA HOSPITAL, UNIVERSITY OF GOTEBORG, GOTEBORG, SWEDEN

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To

Barbro

and

Gunilla, Torbjorn, Lena and Jorgen

From the Swedish
by
HELEN FREY

GÖTEBORG 1966
ELANDERS BOKTRYCKERI AKTIEBOLAG

CONTENTS

INTRODUCTION

> On dira que l'age le sexe le tempérament l'idiosyncrasie l'etat de veille de sommeil, d'exercice de repos de sante de maladies, les passions modifient plus ou moins la force du coeur
>
> Poiseuille 1828

Only a few decades ago little was known about the hemodynamics in arterial hypertension. Today with the development of methods of catheterizing the heart and blood vessels and of more exact means of analysis it is possible to obtain much more information than before on the hemodynamic alterations occurring in cardiovascular disease

As a result of this there have been several reports during recent years on the hemodynamics in arterial hypertension But much more needs to be known before the picture is clear An expert committee appointed by the World Health Organization (2) to recommend avenues of research in arterial hypertension among other things stressed the importance of continued study of the hemodynamics in essential hypertension in man and in experimental hypertension in animals

It would mean a large step forward if we were able to plot the natural history of arterial hypertension in terms of hemodynamics The major question here is whether the hypertension begins with a rise in the vascular resistance in the systemic circulation, or with an increase in the flow of blood A definite answer to this question would provide many profitable clues for research on the pathogenesis of the disease Similarly, clear knowledge of the hemodynamic conditions at different stages of the disease would enable us to provide for more efficacious treatment than is possible today

Values for the blood pressure and blood flow in arterial hypertension determined only from patients in the resting state do not give complete information on the degree of circulatory disorder and they are subject to the errors associated with deviations from the true basal state at the time of examination. More information on the state of the circulation is obtained by examining the subjects under different kinds of stress It is for this reason the observations at rest are often complemented with those made when the subjects are under different forms of mental or physical strain

The present study is a report on the cardiac output and arterial blood pressure at rest and during exercise in the sitting position of 99 men and women with arterial hypertension of various stages The results from these subjects were compared with the same data from 87 apparently normotensive persons These control subjects were not selected to represent the general population. The main purpose of the investigation was to compare hypertensive subjects with subjects with no cardiovascular disease and to study how a rise in arterial blood pressure affects the systemic circulation

(45) observed a high cardiac output at rest not only in subjects with mild arterial hypertension but also in ones with severe *hypertension*

The heart rate at rest of hypertensive patients showing no signs of heart failure but with established arterial hyper tension is said to be no different from that of control subjects (11 18 45 46 75 100 120, 137 146) Some have noted that a hyperkinetic circulation with a rapid heart rate is common in early *uncomplicated arterial hypertension* (94 131 154) but others have not noted anything special in the heart rate in their series (11 45 75)

The stroke volume at rest in the supine position in established arterial hyper tension without signs of decompensation is usually found to be the same as that of normotensive subjects (45 78 100 137 147) But a reduced stroke volume has been reported in severe cases *especially in ones of heart failure* (11 58 75 78 100 125 137, 146 147) The stroke volume in early uncomplicated forms of arterial hypertension has been reported to be raised (11, 45 75, 154) or unchanged (58) in comparison with control groups Patients with labile arterial hypertension and a high cardiac output at rest are reported to have a higher stroke volume than ones with a normal cardiac output (33) An increase in both the stroke *volume* and cardiac output has been found *in acute glomerulo* nephritis (29)

The oxygen consumption and arterio-venous oxygen difference at rest in the supine position are said to be the same in hypertensive subjects as in normotensive subjects (18 94 100 137, 146) though it has been observed *that they tend to* rise in patients suffering from exertional dyspnea and left ventricular failure (100, 125 137 146 152) A rise in the basal metabolic rate however, may occur in euthyroid *hypertensive subjects*, even when there is no decompensation (46 120 152) Other observations have been a wide arteriovenous oxygen difference in hypertensive subjects without heart failure (120) and a narrow difference in subjects with early uncomplicated arterial hypertension (94 152)

Most authors are of the opinion that the extracellular space and the volume of circulating blood are of the same magnitude in subjects with established arterial hypertension of both the renal and essential type but without heart failure as in normotensive subjects (26 30 36 45 46, 50 59 87 141) But some report both lower (11 78 117) and higher (58 138) values than in control subjects *According to one investigation*, the blood volume is larger in severe hypertension than in milder forms of the disease (45) An increase in the volume of circulating blood has also been reported in patients with early uncomplicated essential hyper tension (58) acute glomerulonephritis (35 59) and *primary aldosteronism* with arterial hypertension (14) Hemato *crit readings (18 36 45 54 58, 87)* and values for *blood* viscosity (54 112) have generally not shown any definite differences between hypertensive and normotensive persons Some authors (141), however found higher values for hema tocrit and viscosity in a small group of hypertensive middle aged men than in a control group

SURVEY OF LITERATURE

After Bright (20) noted the connection between enlargement of the heart and kidney disease, varying theories were evolved on the part played by the heart in the genesis and course of arterial hypertension One theory, that of Geigel (56), was that an increase in cardiac activity might play a cardinal part

The discovery by Goldblatt *et al* (60) that experimental hypertension could be produced with renal ischemia, focussed attention on the kidneys, and later it was shown that the cardiac output in established arterial hypertension did not differ from that in normotensive persons (63) After this, it became the current opinion that an increase in the systemic vascular resistance was the main hemodynamic alteration in most hypertensive persons (51, 63)

Lately attention has swung back to the part played by the heart in arterial hypertension, especially during the early stages (23, 98)

Observations at rest

Not until clinical methods for catheterizing the heart were evolved was it possible to obtain reliable information on the size of the cardiac output in arterial hypertension Much earlier however several investigators to begin with Plesch (114), reported finding normal or subnormal values for cardiac output on indirect measurement

Goldring & Chasis (63) were the first to use catheterization of the right side of the heart and Fick's principle for measuring the cardiac output Examining 6 hypertensive subjects in the supine position and finding that they did not differ from a control group, they concluded that the systemic vascular resistance was increased in these subjects, probably because of a reduction in the cross sectional area of the peripheral vascular bed After their report, other authors reported similar observations in hypertensive patients without heart failure examined in the same way, some of these authors used Fick's principle (18, 100, 137, 146, 152), some dye dilution technics (21, 45, 58), and others quantitative radiocardiography (22)

Hypertensive subjects with clinical signs of left ventricular heart failure generally show a low cardiac output (76 78, 100, 125, 137, 146, 152) Some authors have reported a low output also in patients showing no signs of heart failure (11, 22 58 75 78, 120 158)

But this pattern—a normal or low cardiac output and increased systemic vascular resistance at rest—is not present in all cases of arterial hypertension Thus a high cardiac output and a normal systemic vascular resistance have been observed in patients with early uncomplicated hypertension resting in the supine position (11 22, 33 94 131 146 152 154) The same hemodynamic pattern has been observed in acute glomerulonephritis (29, 59) One group

(45) observed a high cardiac output at rest not only in subjects with mild arterial hypertension but also in ones with severe hypertension

The heart rate at rest of hypertensive patients showing no signs of heart failure but with established arterial hypertension is said to be no different from that of control subjects (11, 18, 45 46 75 100 120 137, 146) Some have noted that a hyperkinetic circulation with a rapid heart rate is common in early uncomplicated arterial hypertension (94 131 154) but others have not noted anything special in the heart rate in their series (11 45 75)

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Most authors are of the opinion that the extracellular space and the volume of circulating blood are of the same magnitude in subjects with established arterial hypertension of both the renal and essential type, but without heart failure, as in normotensive subjects (26, 30 36 45 46 50 59, 87, 141) But some report both lower (11 78 117) and higher (59 138) values than in control subjects According to one investigation the blood volume is larger in severe hypertension than in milder forms of the disease (45) An increase in the volume of circulating blood has also been reported in patients with early uncomplicated essential hypertension (58) acute glomerulonephritis (35 59) and primary aldosteronism with arterial hypertension (14) Hematocrit readings (18 36 45 54, 58 87) and values for blood viscosity (54 112) have generally not shown any definite differences between hypertensive and normotensive persons Some authors (141) however found higher values for hematocrit and viscosity in a small group of hypertensive middle aged men than in a control group

After Bright (20) noted the connection between enlargement of the heart and kidney disease, varying theories were evolved on the part played by the heart in the genesis and course of arterial hypertension One theory, that of Geigel (56), was that an increase in cardiac activity might play a cardinal part

The discovery by Goldblatt *et al* (60) that experimental hypertension could be produced with renal ischemia, focussed attention on the kidneys, and later it was shown that the cardiac output in established arterial hypertension did not differ from that in normotensive persons (63) After this, it became the current opinion that an increase in the systemic vascular resistance was the main hemo dynamic alteration in most hypertensive persons (51, 63)

Lately attention has swung back to the part played by the heart in arterial hypertension, especially during the early stages (23, 98)

Observations at rest

Not until clinical methods for catheterizing the heart were evolved was it possible to obtain reliable information on the size of the cardiac output in arterial hypertension Much earlier, however several investigators to begin with Plesch (114), reported finding normal or subnormal values for cardiac output on indirect measurement

Goldring & Chasis (63) were the first to use catheterization of the right side of the heart and Fick's principle for measuring the cardiac output Examining 6 hypertensive subjects in the supine position and finding that they did not differ from a control group, they concluded that the systemic vascular resistance was increased in these subjects probably because of a reduction in the cross sectional area of the peripheral vascular bed After their report, other authors reported similar observations in hypertensive patients without heart failure examined in the same way, some of these authors used Fick's principle (18, 100, 137, 146 152), some dye dilution technics (21, 45, 58) and others quantitative radiocardiography (22)

Hypertensive subjects with clinical signs of left ventricular heart failure generally show a low cardiac output (76 78, 100 125, 137 146 152) Some authors have reported a low output also in patients showing no signs of heart failure (11 22 58 75 78 120 158)

But this pattern — a normal or low cardiac output and increased systemic vascular resistance at rest — is not present in all cases of arterial hypertension Thus a high cardiac output and a normal systemic vascular resistance have been observed in patients with early un complicated hypertension resting in the supine position (11 22 33, 94 131 146, 152 154) The same hemodynamic pattern has been observed in acute glomerulonephritis (29, 59) One group

The response of the stroke volume to exercise in the supine position is usually said to be the same in hypertensive patients without heart failure as in healthy subjects (100, 137, 146, 158) One series of patients with early uncomplicated hypertension, however showed a much larger increase in stroke volume during exercise than control subjects (94) Hypertensive subjects with signs of decompensation on the other hand have shown a smaller rise or a reduction in the stroke volume during exercise in comparison with control subjects (100 137)

As to the response of the systemic vascular resistance to exercise according to one study of subjects exercising in the supine position the resistance falls about the same amount in exercising hypertensive subjects with and without severe exertional dyspnea as it does in exercising control subjects (137) In another study hypertensive subjects had higher values than control subjects during exercise as well as rest (146)

The arteriovenous oxygen difference during exercise according to a number of authors examining subjects in the supine position widens to the same extent in hypertensive subjects without heart failure as it does in control subjects (100 137) but to an abnormal extent in hypertensive subjects with heart failure (76 100, 125, 137) Another investigator (146), however, failed to find any connection between functional capacity and the size of the arteriovenous oxygen difference during exercise According to another report, patients with early, uncomplicated hypertension show less widening of the arteriovenous oxygen difference on exercise than control subjects (94)

Little has been published about the effect of exercise on the volume of blood and the hematocrit score in arterial hypertension. In a study of a small group of middle aged men it was noted that their plasma volume fell more on exercise than it did in control subjects but that the hematocrit level rose to about the same extent in both groups (141)

Several authors (9, 38 103 116 139 140 154 155) have studied the hemodynamics in hypertensive subjects after they have done some form of exercise As the circulation probably starts to change almost the moment the subjects *stop exercising* whether they are healthy or hypertensive (24 102 121), the conditions these investigators noted probably do not represent the conditions obtaining during the actual exercise

Observations during and after exercise

After Barath (7) reported in 1928 that the auscultatory blood pressure rose much higher in hypertensive subjects after they climbed stairs than it did in control subjects, several investigations were made of the reaction of hypertensive subjects to physical stress Different forms of exercise have been used for this, from a series of sit ups in bed to graded work on a bicycle ergometer

The relation between the rise in oxygen consumption and the amount of exercise done is said to be the same in subjects with arterial hypertension of different degrees as in normotensive subjects (94, 137)

Little is known about the reaction of the pulse to exercise in arterial hypertension There is one report of a disproportionately large rise in the heart rate during exercise in the supine position in hypertensive subjects, both ones severely disabled by exertional dyspnea and ones who were not (137) But other authors have not noted this reaction, either in early uncomplicated arterial hypertension or in more advanced forms of the disease (24, 94, 100, 141, 146)

That the systolic blood pressure rises distinctly in exercising hypertensive subjects seems to be generally agreed, this has been observed on examination of patients exercising both in the supine and sitting position (4, 24, 32, 39, 57 83, 118, 141, 146) According to some reports, it rises more on exercise than in normotensive subjects, whether the patients have early, uncomplicated hypertension or established hypertension (32, 94, 102, 118, 146, 158) But other authors (4, 24, 141) have found a lower, rather than higher, percentage rise in hypertensive subjects than in normotensive subjects According to one report (137), hypertensive subjects disabled by exertional dyspnea show a larger rise in systolic blood pressure during exercise in the supine position than do ones who are less disabled, but in another study no correlation was observed between functional group and amount of rise in pressure (146)

Reports vary more on the response of the diastolic pressure to exercise Some authors (32, 57, 94, 146) have noted a distinct rise in hypertensive subjects greater when they were severely disabled than when they had only mild exertional dyspnea (137) Others (4, 39, 83, 102 118, 141) have observed no rise at all, or the same rise as in control groups

All the studies so far on the response of the cardiac output to exercise in arterial hypertension have been done with the subjects lying down According to these, 'compensated" patients respond about the same way in this respect as normotensive subjects (100, 137 146 158) As to hypertensive patients who show or have shown signs of decompensation, while the most common observation is that they do not raise their output as much as control subjects (76 100 125 137) one study found no correlation between the amount the output rose and the functional group to which the patient belonged (146) According to another study, subjects with early uncomplicated hypertension have a higher than normal cardiac output during exercise as well as rest (94)

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PRESENT SERIES

Hypertensive subjects

The present series includes 99 subjects aged between 17 and 64 with arterial hypertension of various degrees Sixty four were men and 35 women, all admitted to the Department of Medicine I at the Sahlgrenska Hospital Most were admitted for the hypertension, but in some the hypertension was discovered after admission for another reason

In each of these 99 subjects, the blood pressure was repeatedly above 150/90 mm Hg on auscultation None of them were taking antihypertensive drugs at the time they were examined for the present study, or had taken any so recently that they were still showing evidence of their hypotensive effect Nor did any have a high blood pressure combined with marked anemia or diabetes or a serious heart disease not associated with the hypertension

Sixty three subjects had never taken a specifically antihypertensive drug The other 36 had Twenty of these 36 had taken them for three months or less Twenty five had stopped taking them three or more weeks before they were examined for the present study and 10 others one to three weeks previously One subject (case 44) had taken 20 mg of pentolinium four times a day until four days before he was examined Four subjects (cases 50, 63, 84, 88) were on maintenance doses of digitalis or quinidine, or both, and 6 others were taking a sedative of some kind at the time of the study

The subjects were examined according to the routine procedure at our department in cases of arterial hypertension physical examination, examination of eyegrounds by an ophthalmologist, 11 lead electrocardiography with the curves evaluated by a clinical physiologist roentgenographic study of the heart and lungs with the films checked by a roentgenologist, intravenous pyelography or renal aortography, or both, as well as routine laboratory analysis of the blood and urine As a rule the auscultatory blood pressure was measured twice a day while the patient was in hospital

The subjects were grouped into three stages of hypertensive disease on the basis of their past history and the clinical observations according to the norms drawn up by the expert committee appointed by the World Health Organization (2) for the classification of arterial hypertension The three stages are as follows

Stage 1 Early arterial hypertension without evidence of organic changes in the cardiovascular system

Stage 2 Established arterial hypertension with signs of cardiovascular hypertrophy but without other evidence of organic damage

Stage 3 Advanced arterial hypertension with evidence of organic damage attributable to the hypertensive disease

The hypertension was classified according to potential cause on the basis of the following criteria

Chronic pyelonephritis A history of attacks of acute pyelonephritis albuminuria and pyuria impaired urinary concentrating ability and changes typical of chronic pyelonephritis in the pyelogram

Chronic glomerulonephritis A history of acute glomerulonephritis albuminuria and hematuria

Polycystic kidneys Changes in the pyelogram typical of polycystic kidneys

Renovascular hypertension Roentgenographically demonstrable narrowing of one or both renal arteries either through local abnormality or abnormality of generalized nature as in the case of fibromuscular hyperplasia

Post toxemic hypertension Onset of hypertension during pregnancy accompanied by proteinuria

Essential arterial hypertension All the cases which could not be referred to any of the foregoing groups or to any other conceivable cause such as coarctation of the aorta or aldosteronism

Tables I and II in the appendix give the particulars in these respects for the separate subjects as well as their age, the usual anthropometric data and some of the clinical data

Dividing the patients by sex and stage of hypertension gave groups characterized as follows The group means for age anthropometric variables and heart volume are shown in table 1

Hypertensive men Stage 1 This group comprised 14 men between the ages of 17 and 58

TABLE I Age anthropometric data and heart volume for the hypertensive subjects
Means standard errors and standard deviations

		Age	Height cm	Weight kg	BSA m^2	Heart volume ml per m^2 BSA
Stage 1	Men	34 9±4 0	175 5±1 7	71 5±2 5	1 861±0 032	365±18
	n=14	15 1	6 4	9 3	0 119	66
	Women	39 0±7 2	162 8±3 6	64±4 1	1 623±0 0 5	340±11
	n=4	14 3	7 1	8 1	0 151	22
Stage 2	Men	47 3±1 2	175 1±0 9	81 6±2 3	1 967±0 0 7	420±8
	n=37	7 3	5 5	13 9	0 164	49
	Women	47 0±2.2	160 8±1 3	66 4±3 2	1 694±0 034	356±12
	n=17	8 9	5 2	13 0	0 140	48
Stage 3	Men	49 9±2.6	177 1±1 5	8 3±3 1	1 948±0 042	473±38
	n=13	9 3	5 5	11 0	0 152	137
	Women	50.1±2 0	163.5±1 7	63.8±2 0	1 738±0 02	446±26
	n=14	7 4	6 4	7 6	0 100	97

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	Women	4[illegible] 0±2 2	160 8±1 3	66 4±3 2	1 694±0 034	356±12
	n=1[illegible]	8 9	5 3	13 0	0 140	48
Stage 3	Men	49 0±2 6	177 1±1 5	78 3±3 1	1 948±0 042	473±38
	n=13	9 5	5 5	11 0	0 152	137
	Women	50 1±2 0	163 5±1 [illegible]	66 8±2 0	1 [illegible]38±0 027	446±26
	n=14	7 4	6 4	7 6	0 100	97

In 13 cases the hypertension was classed as essential, this includes one case (14) in which the kidneys were not examined roentgenographically One patient (case 3) had chronic glomerulo nephritis

Uncomplicated gastrointestinal bleeding had occurred in 1 case (12) shortly before the study, but all troubles of this nature had disappeared at the time of the studies

Three of the men had received anti hypertensive medication but had stopped taking the drugs three weeks or more before the present studies

The men in this group had been in hospital for 1 to 14 days at the time of the studies, for 4 4 days on the average

Hypertensive men, Stage 2 This group comprised 37 men between the ages of 25 and 58

In 30 cases the hypertension was classified as essential, this includes one case (29) in which the kidneys had not been examined roentgenographically One patient (case 40) was diagnosed as chronic pyelonephritis, and 2 (cases 17, 34) as chronic glomerulonephritis One patient (case 30) had polycystic kidneys and 3 others (cases 23, 44, 51) were classed as renovascular hypertension

Other clinical data of note were a history of renal calculi in 4 cases (17, 38, 41, 46), roentgenographic signs of healed pulmonary tuberculosis in 2 cases (25, 41), roentgenographic signs of pulmonary emphysema in 1 case (51), mild diabetes in 3 cases (39, 43, 44), uncomplicated gastrointestinal bleeding a short while before but no troubles of this kind at the time of the studies in 2 cases (40, 51), an operation many years before for toxic goiter in 1 case (31) and mild hyperthyroidism in 1 (case 45) One patient had been treated for polycythemia a few years previously (case 42)

Twelve men had taken antihypertensive drugs previously; 1 (case 44) had stopped less than a week before the studies, 4 (cases 18, 37, 48, 49) one to three weeks before, and 7 more than three weeks before

In 1 case of converted atrial fibrillation (case 50) the patient was on maintenance doses of digitoxin and quinidine at the time of the studies Two others (cases 18, 41) were taking a sedative of some kind

The men in this group had been in hospital between 1 and 20 days at the time of the studies, for 4 7 days on the average One man (case 17) was examined as an out patient after he had been discharged home convalescent

Hypertensive men, Stage 3 This group comprised 13 men between the ages of 34 and 64

In 11 cases the hypertension was classified as essential Two subjects (cases 54, 58) were diagnosed as chronic glomerulonephritis

Other clinical data of note were a history of renal calculi in 1 case (52), a roentgenographic picture typical of healed pulmonary tuberculosis in 2 cases (57, 59) gastrointestinal bleeding shortly before but which had disappeared by the time of the studies in 1 case (53)

One man (case 55) had shown signs of hypertensive encephalopathy and another (case 56) signs of the Wallenberg syndrome a few years previously There was a history of myocardial infarction in 2 cases (60 61), and a history of angina pectoris

in the same 2 plus another (57) One man (case 63) had atrial fibrillation and a history of left ventricular failure and was taking digitoxin at the time of the studies

In 7 cases (54 56, 57 58 60 63, 64) the serum creatinine exceeded 1 2 mg per 100 ml the highest value was 3 0 mg (case 54) In 1 case (56) the hemoglobin measured less than 11 g per hundred ml of blood amounting to 10 4 g

Eight men had taken antihypertensive drugs Four of them (cases 52, 55, 59 64) stopped one or two weeks before the studies the others more than three weeks before Two men (cases 54 64) were taking some kind of a sedative at the time of the studies

The men in this group had been in hospital for 2 to 20 days at the time of the studies for 7 4 days on the average

Hypertensive women Stage 1 This group comprised 4 women between the ages of 23 and 53

One woman (case 66) had post toxemic hypertension the others were classified as essential hypertension One woman (case 68) had had rheumatic fever when she was a girl

None of the four had had any anti hypertensive therapy One woman (case 68) was taking a mild sedative at the time of the studies

The women in this group had been in hospital for 1 to 14 days at the time of the studies for 5 3 days on the average

Hypertensive women Stage 2 This group comprised 17 women between the ages of 32 and 61

In 8 cases the hypertension was classified as essential 5 subjects (cases 78 79 81, 83, 84) were diagnosed as chronic pyelonephritis 2 (cases 74, 85) as renovascular hypertension and 2 (cases 70, 71) as post toxemic hypertension

Other clinical data of note were a history of bilateral pulmonary tuberculosis in 1 case (74), an operation several years ago for nontoxic goiter in 1 case (78) radiation for cancer of the uterine cervix in 1 case (85), and uncomplicated gastro intestinal bleeding shortly before but which had disappeared by the time of the studies in 1 case (83)

Eight women had taken antihyperten sive drugs One (case 82) had stopped a week before the studies the others more than three weeks before

One woman (case 84) was on a main tenance dose of digitoxin at the time of the studies Another (case 73) was taking a sedative

The women in this group had been in hospital for 3 to 24 days at the time of the studies for 8 2 days on the average

Hypertensive women Stage 3 This group comprised 14 women between the ages of 38 and 62

In 11 cases the hypertension was classified as essential The group also contained 1 case each of chronic py elonephritis (95), renovascular hyper tension (96) and post toxemic hyper tension (86)

Other clinical data of note were renal calculi in 2 cases (91, 97) rheumatic fever during childhood and signs of mild mitral insufficiency in 1 case (91) mild symptoms of the rheumatoid arthritis type in 1 case (90) multiple arterial strictures in 1 case (94)

A cerebral vascular accident with complete recovery had occurred in 1 case (87) Four women suffered from angina pectoris (cases 86, 90, 92, 95) Two women (cases 88, 89) had a history pointing to left ventricular failure, and 1 of them (case 89) showed mild signs of insufficiency on admission

In 2 cases (91, 94) the serum creatinine exceeded 1 2 mg, the highest value was 1 5 mg (case 94) Hemoglobin values under 11 0 g were noted in 3 cases (86, 92, 93), the lowest value being 10 4 g (case 93)

Five women had taken antihypertensive drugs One (case 95) had stopped nine days before the studies, the others three weeks or more before

One woman (case 88) was on a maintenance dose of digitoxin at the time of the studies

The women in this group had been in hospital for 1 to 20 days, for 7 5 days on the average

Comments The height of the blood pressure depends on many conditions, such as age, sex and weight (84, 107, 113, 142), and the line between normal and elevated must be drawn arbitrarily to a certain extent For the purposes of the present investigation the upper normal limit was drawn at 150/90 mm Hg, figures which are probably a little too high for young subjects and a little too low for old subjects They coincide with the opinion of many authors (46 63, 96, 97), however and seem to be the values which most authors studying the circulation in arterial hypertension have taken as the upper limit for normal (11, 30, 36, 45, 54, 116, 126, 139, 140) Some authors (6, 22, 34, 71, 72, 74, 146, 158) have preferred a lower limit for the systolic pressure—140 or 145 mm Hg Others (103, 154) have put the upper limit for the normal diastolic pressure higher, or at 100 mm Hg One investigator put the upper limit at 150/90 mm Hg for persons under 30 and at 150/100 for older persons (33)

The electrocardiographic criteria laid down by Sokolow & Lyon (132) and Goldman (62) were taken to indicate left ventricular hypertrophy and strain Left axis deviation or elevated *R* waves over the left ventricle without any other abnormalities were not considered to point to left ventricular hypertrophy as these may be shown by persons without any cardiovascular disease (84 93)

The roentgenograms of the heart and lungs were taken according to the routine procedure at the hospital The volume of the heart was reckoned according to Jonsell's method (88) The upper normal limit for this volume was put at 450 ml per square meter body surface for men and at 400 ml for women, regardless of variations associated with age (84) The usual roentgenographic principles were used for judging the configuration of the heart (82 106)

Abnormalities in the retinal vessels were graded according to the principles originally laid down by Keith Wagener & Baker (92) Whenever there was any doubt they were graded in the lower of the two grades in question

Whenever a conceivable cause for the hypertension could be found in the present cases this is reported But the presence of a conceivable cause does not always mean that it led to the hyper

tension Thus it has been discussed whether there is any causal connection between chronic pyelonephritis and hyper tension (130) and some subjects with *renal artery stenosis are persistently* normotensive (115) Again it is often hard to distinguish between post toxemic and essential hypertension (8 46)

Authors dividing hypertensive patients into different groups according to the *severity* of the disease have followed different principles for doing so In studies of hemodynamics some have divided them into ones with and without heart failure (78 152) some according to whether or not severe exertional dyspnea was present (137) one according to the functional groups described by the New York Heart Association (146) some according to the classification schemes of Smithwick (120) and Myasni kov (58) some according to whether the hypertension was fixed or labile (45 116) and some by still another system In this study the grouping was done according to the system of the World Health Organization which combines many of the aforegoing schemes but which does not seem to have been used before for studies of this kind

Only four of the women patients could be classed as Stage 1 according to this method These are too few to give a representative picture of the hemodyna mics in this category, but their values are reported to give an all round picture

Because of the different methods of classification used it is difficult to compare the results from the reports in the literature with each other and with those from the present study Accordingly whenever the results of previous authors were compared with those in the present study and it was not possible to use their own terminology for the purpose an attempt was made to regroup their subjects according to the principles described by the World Health Organization

Control subjects

Eighty seven control subjects were examined with the same methods as the hypertensive subjects Detailed results from this group will be reported separately in collaboration with Cramér Malmcrona, Schroder & Varnauskas

None of the control subjects had any clinical signs or symptoms of cardio vascular disease or other diseases of relevance to the investigation None had a casual auscultatory *blood pressure* above 150/90 mm Hg The majority

TABLE 7 Age and anthropometric data for the control subjects
Means standard errors and standard deviations

	Age	Height cm	Weight kg	BSA m^2
Men $n = 59$	33 6±1 5 11 3	178 8±0 8 5 9	[illegible] 8±1 12 7	1 935±0 021 0 159
Women $n = 28$	36 3±2 [illegible] 11 6	165 3±1 0 [illegible] 3	64 6±1 6 8.4	1 [illegible]08±0 024 0 1[illegible]4

61 altogether, were healthy volunteers paid to participate, coming from a wide range of occupations and social classes The other 26 were patients at the hospital with mild signs and symptoms, if any, of disease

Fifty nine were men between the ages of 16 and 59 (table 2), 18 were in the hospital at the time of the studies The other 28 were women between 18 and 56, 8 were in hospital at the time of the studies

Comments The reason for choosing 150/90 mm Hg as the upper limit for normal blood pressure is given in the foregoing section on the hypertensive subjects

The majority of the control subjects lived at home, while all except one of the hypertensive subjects were in hospital at the time of the studies This probably made no difference to a comparison between the results of the two series If anything, the fact that most of the control subjects had not rested in hospital before the studies would increase the significance of any difference between them and the hypertensive subjects in values for blood pressure and in the response of the pressure to strain

All the subjects were studied in the morning in the fasting state None received any premedication

Under local anesthesia a 40 cm long No 205 polyethylene catheter was inserted percutaneously 10 to 15 cm up in the brachial artery, according to the method described by Seldinger (124) The catheter was sluiced intermittently with physiologic saline solution containing 5000 I U of heparin per 1000 ml

Another catheter was inserted the same way into an antecubital vein. In 73 cases a roentgenographically opaque, thin walled Ödman Ledin catheter (Kifa AB Sweden) was introduced into the upper part of the right atrium or superior vena cava with its proximal tip kept under fluoroscopic control In the other 26 cases a No 160 polyethylene tube was inserted up to the level of the subclavian vein The venous catheter was kept open with a slow drip of saline solution containing heparin

The procedure was explained to the subjects beforehand and every effort was made to cause as little discomfort as possible After the tubes were inserted about a half an hour was allowed to pass before the first measurements were made

Then with the subjects sitting comfortably in an armchair the heart rate intra arterial blood pressure cardiac output and oxygen consumption were measured To study the reproducibility of the determinations with reference both to biologic variation and to the laboratory methods used, repeat resting measurements were made 10 to 15 minutes later in 20 hypertensive subjects, 11 men and 9 women

The effect of exercise was studied with the subjects sitting on an electrically braked variable load bicycle ergometer (Elema Schonander AB, Sweden) of the type described by Holmgren & Mattsson (81) The rate of pedalling, which could be read off on a tachometer was set at 60 revolutions a minute Minor variations in the rate made little difference for the bicycle ergometer is equipped with a special generator so constructed that the subjects do the same amount of work at whatever rate they pedal between 45 and 75 revolutions a minute

The level of exercise was adapted to the subject s tolerance from 200 to 1200 kpm/min for the men and from 150 to 400 kpm/min. for the women Thirty six of the hypertensive subjects 25 men and 11 women did one period of exercise at a level slightly under what it was assumed the subject could stand In the other 63 cases, 39 men and 24 women a lower level was chosen to start with Thirty two of these 63, 20 men and 12 women exercised again after having rested for 15 to 20 minutes sitting down, and then as a rule at a level just below what was assumed to be their upper limit of tolerance The other 31 subjects 19 men and 12 women did not go on to a second period either

because their blood pressure rose markedly, or because they would not cooperate, or for some other reason

To study the reproducibility of the measurements made during exercise, 11 hypertensive subjects, 7 men and 4 women, exercised for two periods at the same level, with 15 or 20 minutes rest between

During the exercising, each period lasting about 10 or 12 minutes, the heart rate and blood pressure were measured after 1, 3, 5, 7, 8 and 11 minutes Sometimes, when a high level of exercise was used, the subjects could not last out the period, but in no case did they exercise for less than five minutes

Collection of expired air for measurement of the oxygen consumption was usually begun after the subject had been exercising for 4 to 6 minutes The cardiac output was measured after the subject had exercised for 9 or 10 minutes as a rule For technical reasons values for the oxygen consumption are lacking for 5 hypertensive subjects both at rest and during exercise The values during exercise for one period are lacking for 9 hypertensive subjects, 5 men and 4 women, because they could not keep the mouth piece on properly, and for 3 cases for the second exercising period Determination of the resting cardiac output was a failure in 1 case, and during one period of exercise in 2 cases

No serious complication developed in any case during the study Some subjects felt faint after they stopped exercising or while the tubes were being removed One hypertensive man complained of a feeling of oppression on his chest immediately after the dye was injected, perhaps because he was hypersensitive to the bromsulphalein One hypertensive woman got a transient fever peak the afternoon after the study, perhaps caused by pyrogens In a few cases the radial pulse was weakened for a day or so after the study, and a few subjects got thrombophlebitis in their upper arms

Laboratory methods and calculations

Oxygen consumption ($=V_{O_2}$) The subject was connected to a valvular system with a low resistance and the expired air collected in a Douglas bag The total ventilation was determined with a gasometer and double analysis was done of the content of oxygen and carbon dioxide according to the method described by Scholander (122) The values for oxygen consumption were expressed in liters per minute STPD

Heart rate ($=HR$) Throughout the study the subjects were connected with a five channel electrocardiograph type EM 130 (AB Elema Sweden) The tracing from a precordial lead was monitored on an oscilloscope and registered photographically every time the pressure was measured and while the cardiac output was being determined At least ten cardiac cycles were used for computing the heart rate in beats per minute

Arterial blood pressure ($=P_{BA}$) The tube in the brachial artery was connected with a pressure transducer of the variable inductance type (EMT 490A Elema Schonander AB) The impulses were led via an amplifier (EMT 405 Elema Schonander AB) to the electrocardiograph and registered photographically It was checked that the registering system was linear in the areas of pressure in question. The fourth intercostal space with the subject sitting was taken as the zero reference level

The systolic ($P_{S_{BA}}$) and diastolic ($P_{D_{BA}}$) blood pressures in mm Hg were reckoned from undamped curves in the manner described by Holmgren (79) The mean arterial pressure ($\bar{P}_{BA}$) was obtained by electrical integration

The resting blood pressure was measured immediately before and after each measurement of the cardiac output and the mean value used to represent the resting blood pressure for the subject in question

As mentioned the pressure was determined several times while the subjects were exercising The value obtained immediately before the cardiac output was taken as representative of the exercising state

Cardiac output ($=\dot{Q}$) The cardiac output was determined with a modification of the dye dilution technic described by Stewart (135) and Hamilton *et al* (69) using bromsulphalein as the indicator in all except one case (73) in which cardiogreen was used Forsberg (48) has described the method used in our laboratory in detail It has been established that bromsulphalein gives values for cardiac output equivalent to those obtained with Fick s principle and other dye indicators such as Evans Blue and cardiogreen (48 109 150)

The dye was injected rapidly into the right atrium or subclavian vein and at

the same time an intermittently rotating blood collector was started, the blood being allowed to run down into small Ellermann tubes for one or two seconds. Three or four seconds after the injection was done, the dye left in the tube was aspirated back into the syringe. The extinction values for bromsulphalein at 580 mμ were read off in a Beckman B spectrophotometer. The dye dilution curve was plotted on semilogarithmic paper, and the downslope extrapolated to zero. The surface under the curve obtained was used for calculating the cardiac output according to the following formula

$$Q \text{ liters/min} = 60 \times \frac{E_i}{E_a} \times \frac{100}{100-Hct}$$

in which Q stands for cardiac output, E_i the amount of dye injected into the circulation and E_a the surface under the extrapolated dye dilution curve.

Stroke volume $(=SV)$. The heart rate measured directly after the injection of the dye was used to calculate the stroke volume in milliliters per beat.

Systemic vascular resistance $(=SVR)$. The quotient obtained by dividing the mean arterial blood pressure in mm Hg by the cardiac output in liters per minute was calculated, and used as an index, expressed in arbitrary units, of the integrated vascular resistance in the systemic circulation.

Systemic vascular conductance $(=SVC)$. The formula $(1/SVR) \times 10^3$ was used to express the systemic vascular conductance in arbitrary units.

Arteriovenous oxygen difference $(=(a-\bar{v})_{O_2})$. The values for oxygen consumption and cardiac output were inserted into Fick's formula (44) to calculate the arteriovenous oxygen difference in milliliters per liter.

Hematocrit $(=Hct)$. The arterial blood was collected in Ellermann tubes. After careful mixing it was transferred to two 50 mm capillary tubes and centrifuged at 6000 revolutions a minute for 15 minutes. The mean of the two determinations was then used to represent the hematocrit score. No correction was made for trapped plasma.

Body surface area $(=BSA)$. A nomogram composed from the DuBois & DuBois formula (31) was used for calculating the surface of the body in square meters.

Statistical methods

All the data from the subjects were fed into a Facit EDB 3 computer for statistical analysis of the results. The conventional statistical methods were used for calculating the mean $(\bar{x})$, the standard deviation of the mean (s_x, s_d) and the standard error of the mean $(s_{\bar{x}}, s_{\bar{d}})$. The difference between means was designated with $\bar{d}$.

When repeat measurements were made at rest and during exercise the percentage systematic error and the error of the single determination were calculated.

The hypertensive subjects differed in amount of physical training and several had seldom been on a bicycle. The response to exercise was therefore studied in terms of *increase in oxygen consumption*. This is a more reliable way of expressing the

amount of work a subject does than in number of kpm/min for well trained subjects respond differently to physical exertion than do untrained subjects (5 12 53) and the degree of mechanical efficiency varies with age (3) Moreover, the braking effect of the bicycle ergometer used changes a little with time with the result that the actual load exerted at the various load settings may vary between calibrations

The difference between the values at rest and during exercise for the various functions were converted to express the difference per rise of one liter in oxygen consumption The slope of the regression line was calculated from the mean change and expressed as an equation In order to be able to analyze all the data statistically, whenever values were missing for a case randomized values were fed into the computer consideration being given to age, sex and level of exercise

The data from the control series were subjected to the same form of statistical analysis In addition, multiple regression analysis with respect to age and anthropometric variables were done for all the functions both at rest and during exercise Before the values from the hypertensive groups and control series were compared the variables for the hypertensive groups were corrected for age and anthropometric data, whenever there were significant regressions between these data and the different functions studied

The Student *t* test was used for testing the significance of differences between hypertensive and control subjects a *p*-value of <0 001 being considered to denote a highly significant difference, of <0 01 a significant difference and of <0 05 an almost significant difference

Systematic error and the error of the single determination

Table 3 shows the results of two consecutive measurements at rest in 20 hypertensive subjects, and table 4 the results from two periods of exercise at the same level in 11 hypertensive subjects

The systolic blood pressure was significantly lower at the second measurement taken during rest, the difference being −3 7 mm Hg The systematic error lay between 0 1 and 3 6 per cent and the error of the single determination between 1 2 and 9 6 per cent

During the second period of exercise the systolic arterial blood pressure rose highly significantly less and the mean arterial blood pressure significantly less Otherwise there were no significant differences between the two periods for the other variables The systematic error lay between 0 3 and 7 1 per cent, and the error of the single determination between 2 0 and 8 2 per cent

Comment Consecutive measurements of the same kind were also made in 14 control subjects These gave the same results on the whole as those in the hypertensive subjects The control subjects showed no difference in systolic blood pressure from the first to the second measurement at rest, but a significant drop in the heart rate

Nor did the control group show a lower arterial blood pressure during the second period of exercise as did the hypertensive subjects On the other hand, they showed significant differences between the two periods of exercise for the heart rate stroke volume and arterio

TABLE 3 Results of two consecutive determinations at rest of various features studied ($n = 20$)

	$\bar{x}_1$	$\bar{x}_2$	$\bar{d}$	$\sigma_{\bar{d}}$	p	Systematic error in per cent	Error of single determination in per cent
V_{O_2}	0 259	0 256	−0 003	0 7		1 1	5 3
HR	79 6	76 8	−2 8	2 0		3 6	5 1
$P_{S_{BA}}$	173 1	169 4	−3 7	2 4	<0 05	2 1	2 8
$P_{D_{BA}}$	94 6	93 3	−1 3	1 6		1 4	2
$\bar{P}_{BA}$	124 2	122 3	−1 9	1 6		1 5	3 0
Q	5 68	5 57	−0 11	0 6		1 9	9 6
SV	72 4	73 7	+1 3	0 6		1 8	8 9
SVR	23 36	23 40	+0 04	0 1		0 2	8 1
$(a-v)O_2$	46 6	46 6	0	0 1		0 1	7 3
Hct	40 6	40 7	+0 1	1 0		0 4	1 2

TABLE 4 Values obtained for various features during two consecutive periods of exercise at same level (n=11)

	x_1	x_2	$\bar{d}$	$s_{\bar{d}}$	p	Systematic error in per cent	Error of single determination in per cent
V_{O_2}	1 404	1 425	+ 0 021	0 9		1 5	3 9
HR	1-6 2	1-7 3	+ 1 1	0 7		0 7	2 5
$P_{S_{BA}}$	242 2	225 1	−17 1	4 7	<0 001	7 1	3 7
$P_{D_{BA}}$	109 7	106 1	− 3 6	1 4		3 3	5 6
$\bar{P}_{BA}$	158 7	147 8	−10 9	3 8	<0 01	6 9	4 5
Q	12 70	12 66	− 0 04	0 1		0 3	7 3
SV	82 5	81 3	− 1 -	0 4		1 4	8 2
SVR	13 54	12 85	− 0 69	1 7		5 1	7 3
$(a-v)_{O_2}$	111 1	112 7	+ 1 6	0 6		1 4	6 0
Hct	43 7	43 0	− 0 7	1 9		1 5	2 0

venous oxygen difference Patients with coronary disease are said to show a lower oxygen consumption during exercise in the supine position after resting for an hour (104) Other reports say that normotensive subjects or subjects with pulmonary disease do not show any change in these functions during a repeat exercise session in the supine position (17 153)

Condition at rest and response to exercise

Oxygen consumption

At rest The hypertensive men at Stage 1 had a higher resting oxygen uptake than the control men the difference being highly significant (table 5) The other hypertensive groups did not differ from the control subjects in this respect

TABLE 5 Oxygen consumption (1/min) at rest

		Mean ± standard error $\bar{x} \pm s_{\bar{x}}$	Mean diff from the controls[1]) $\bar{d}$	Probability p
Stage 1	Men	0 296±0 00-	+0 0-6	<0 001
	Women	0 -07±0 0 9	−0 008	—
Stage 2	Men	0 291±0 007	+0 010	—
	Women	0 -30±0 011	+0 006	—
Stage 3	Men	0 -94±0 008	+0 014	—
	Women	0 -36±0 008	+0 007	—

[1]) Adjusted according to multiple regression functions of the control subjects.
Equations Men $V_{O_2\,rest} = 0\ 081 + 0\ 12{*}1 \times BSA$ Women $V_{O_2\,rest} = 0\ 018 + 0\ 1214 \times BSA$

TABLE 6 Oxygen consumption (l/min.) of hypertensive subjects during *exercise*. *Figures refer* to number of subjects in respective subgroups

		≦0.75	0.76–1.25	1.26–1.75	1.76–2.25	≧2.26
Stage 1	Men			6	[illegible]	1
	Women		3	1		
Stage 2	Men		3	20	6	4
	Women	1	8	3		
Stage 3	Men		4	2	3	
	Women		11	1		

Response to exercise. All the hypertensive subjects raised their oxygen consumption during exercise, and did not differ clearly from the control subjects in relationship between oxygen uptake and level of exercise.

Most of the male hypertensive subjects consumed more than 1.25 liters of oxygen a minute during the highest level of exercise allowed in their case (table 6). Only 1 consumed less than 1 liter a minute. In the cases where figures for oxygen consumption are lacking the heart rate exceeded 150 per minute during the most strenuous period of exercise.

All but one female hypertensive subject consumed more than 0.75 liters of oxygen a minute during the most strenuous exercise allowed (table 6). In the cases where figures for oxygen consumption are lacking, all but one had a heart rate above 150 per minute during the period of most strenuous exercise.

Comments. The Stage 2 and 3 men and women did not differ from the control subjects in oxygen consumption at rest. This agrees with the observations of other authors (46, 123, 137, 146).

The men with early hypertension had a higher oxygen uptake at *rest than the* control subjects. The Stage 1 *women* did not, but as there were only 4 of them, no conclusions can be drawn about a sex difference.

The literature contains only a few reports on the resting oxygen consumption in early arterial hypertension. The subjects Konig *et al.* (94) studied did not differ in this respect from a control group, but the patients with systolic arterial hypertension described by Werko & Lagerlof (152) consumed about 20 per cent more oxygen at rest than expected. Rowe *et al.* (120) comparing subjects grouped according to the Smithwick criteria, found that grade 1 and 2 subjects consumed significantly more oxygen at rest than grade 3 and 4 subjects. Their grade 1 and 2 subjects also consumed significantly more — 9 per cent — than their control subjects.

There are also only a few reports on the oxygen consumption of hypertensive subjects during exercise (76, 89, 94, 100, 137, 146). In one investigation (94) the relationship between oxygen uptake and level of exercise was the same in

TABLE 7 Heart rate (beats per minute) at rest

		Mean ± standard error $x \pm s_{\bar{x}}$	Mean diff from the controls $\bar{d}$	Probability p
Stage 1	Men	82 5 ± 4 1	+15 5	<0 001
	Women	79 3 ± 10 0	+10 0	—
Stage 2	Men	69 2 ± 2 1	+ 2 -	—
	Women	82 6 ± 2 3	+13 3	<0 001
Stage 3	Men	69 8 ± 2 6	+ 2 8	—
	Women	76 9 ± 1 4	+ 7 6	<0 01

subjects with early arterial hypertension as in control subjects and in another (137) the same was noted of subjects with more severe hypertension

In most of these investigations the subjects were only required to do mild forms of exercise Only in two (94 137) did they have to work so hard that their oxygen uptake exceeded a liter a minute In other studies in which the subjects were examined with graded exercise but *in which the oxygen uptake* was not registered during the different phases the maximum stress exerted by the exercise ranged between 300 and 600 kpm min (32 83 141) and between 100 and 150 watts (102 118)

Heart rate

At rest The Stage 1 men had a highly significantly greater heart rate at rest than the control men (table 7) The mean rate in the other two groups of men did not *differ* from that of the control men

All three groups of hypertensive women had higher average heart rates at rest than did the *control* women (table 7) the Stage 2 and 3 women having significantly higher rates

Response to exercise The Stage 1 men had *relatively* the same *high heart rate* during *exercise* as during rest (fig 1), and *on exercise the heart rate increased* to the same order in them as in the control men. The Stage 2 men raised their rate more than the control subjects the difference being almost significant, and the Stage 3 men raised their rate significantly higher

A significantly higher rise was also noted in the Stage 3 women and *one* that was almost *significant in the Stage* 1 women (fig 1) The Stage 2 women also increased their rate more than the *control women* but did not differ significantly from them in this respect

Comments It is the general opinion that the resting heart rate in subjects with established or advanced arterial hypertension does not differ particularly from that of normotensive subjects (11 18 45 100 120 137 146) and this is *con*firmed by the data from the *Stage* 2 and 3 men from this study

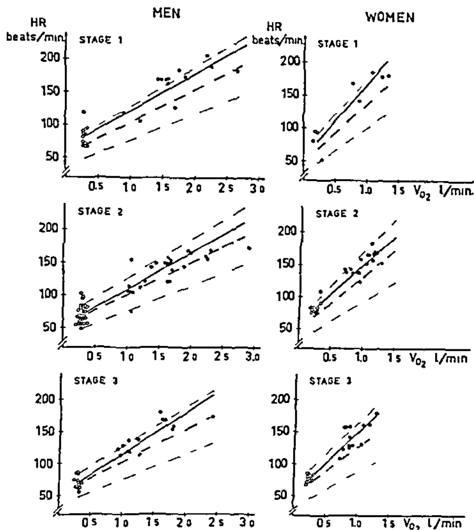

Fig 1 Heart rate Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1]	Significance level of difference
Stage 1	Men	$\hat{y}_x = 65.8 + 56.3\,x$	$\hat{y}_x = 57.5 + 49.9\,x$	–
	Women	$y_x = 55.5 + 114.8\,x$	$y_x = 50.1 + 89.1\,x$	<0.05
Stage 2	Men	$y_x = 52.5 + 57.3\,x$	$y_x = 53.0 + 49.9\,x$	<0.05
	Women	$y_x = 62.2 + 88.7\,x$	$y_x = 51.2 + 80.9\,x$	–
Stage 3	Men	$y_x = 50.6 + 65.4\,x$	$y_x = 53.0 + 49.9\,x$	<0.01
	Women	$y_x = 53.6 + 98.9\,x$	$y_x = 51.9 + 75.9\,x$	<0.01

○ = at rest ● = during exercise solid lines = regressions for hypertensive subjects broken lines = regressions together with $\pm 2s_x$ for control subjects

[1]) The equations adjusted according to multiple regression functions of the control subjects. Equations

Men $V_{O_2\,rest} = 0.061 - 0.1121 \times BSA$

Women $V_{O_2\,rest} = 0.018 + 0.1214 \times BSA$ $\Delta HR/\Delta V_{O_2} = 275.4 - 114.8 \times BSA$

Reports vary on the resting rate in early arterial hypertension The high resting rate in the Stage 1 men reported here tallies with the observations of Thomas (140) Widimsky et al (154) and Konig et al (94) made in patients in the supine position Other authors (11 45 103) have found no difference between the resting heart rate in the supine position of patients with early and established arterial hypertension

Unlike the men the female hypertensive subjects had a higher resting rate than the control women the Stage 2 and 3 women a significantly higher rate Only one previous investigator has divided his subjects by sex (24) he found no difference between the resting pulse rate of hypertensive men and women

That hypertensive subjects raise their heart rates proportionately more on exercise than do normotensive subjects has already been demonstrated by Taylor et al (137) their observations in subjects exercising in the supine position correspond with the observations in the Stage 2 and 3 subjects reported here Lewis et al (100) and Varnauskas (146) on the other hand found no difference between normal and hypertensive subjects with or without signs of cardiac failure in their heart rate during exercise in the supine position

The Stage 1 *women* also raised their heart rate more during exercise than did the control subjects The Stage 1 men did not the difference between them and the control men remaining about the same as during rest Konig et al (94) observed a normal rise in heart rate in a small series of young men with 'hypertensive regulation disorder as long as the exercise caused 140 beats or under but on a higher level of exercise the patients raised their rate less than did control subjects No report has been published on the effect of exercise on the heart rate in early hypertension in women

Brachial artery blood pressure

At rest In all the hypertensive groups of both sexes the means for the resting systolic diastolic and mean arterial pressure in the brachial artery were significantly or highly significantly above those for the control groups (tables 8—10)

TABLE 8 Systolic brachial artery pressure (mm Hg) at rest

		Mean ± standard error $\bar{x} \pm \sigma_{\bar{x}}$	Mean diff from the controls $\bar{d}$	Probability p
Stage 1	Men	147 1 ± 3 8	+22 6	<0 001
	Women	178 0 ± 7 2	+52 1[1]	<0 001
Stage 2	Men	177 [illegible] ± 4 2	+[illegible]2 7	<0 001
	Women	193 9 ± 9 [illegible]	+66 3[1]	<0 001
Stage 3	Men	194 6 ± [illegible] 4	+70 1	<0 001
	Women	187 9 ± 11 3	+56 9[1]	<0 001

[1]) Adjusted according to multiple regression functions of the control subjects
Equation $P_{S_{a.arm}} = 108\ 2 + 0$ [illegible] $6 \times Age$

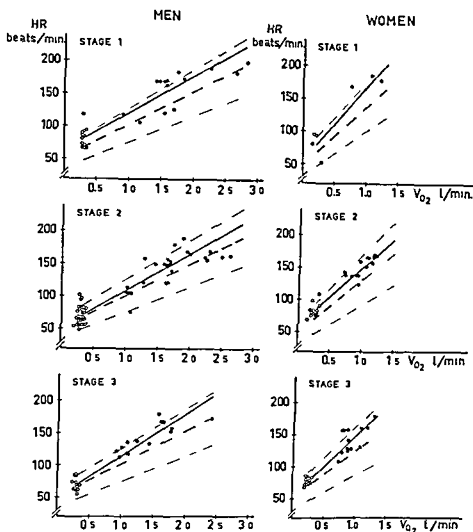

Fig 1 Heart rate Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1]	Significance level of difference
Stage 1	Men	$y_x = 65\ 8 + 56\ 3\ x$	$y_x = 53\ 5 + 49\ 9\ x$	—
	Women	$y_x = 55\ 5 + 114\ 8\ x$	$y_x = 50\ 1 + 59\ 1\ x$	$< 0\ 05$
Stage 2	Men	$y_x = 52\ 5 + 57\ 3\ x$	$y_x = 53\ 0 + 49\ 9\ x$	$< 0\ 05$
	Women	$y_x = 62\ 2 + 58\ 7\ x$	$y_x = 51\ 2 + 50\ 9\ x$	—
Stage 3	Men	$y_x = 50\ 6 + 65\ 4\ x$	$y_x = 53\ 0 + 49\ 9\ x$	$< 0\ 01$
	Women	$y_x = 53\ 6 + 98\ 9\ x$	$y_x = 51\ 9 + 75\ 9\ x$	$< 0\ 01$

○ = at rest ● = during exercise solid lines = regressions for hypertensive subjects broken lines = regressions together with $\pm 2s_x$ for control subjects

[1]) The equations adjusted according to multiple regression functions of the control subjects Equations

Men $\dot{V}_{O_2\ rest} = 0\ 061 + 0\ 1121 \times BSA$

Women $\dot{V}_{O_2\ rest} = 0\ 018 + 0\ 1214 \times BSA$ $\Delta HR / + 1\ 0\ l\ \dot{V}_{O_2} = 275\ 4 - 114\ 8 \times BSA$

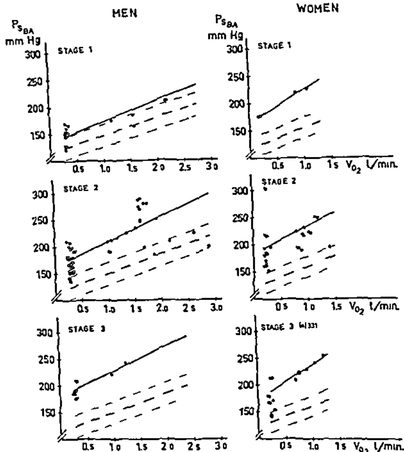

Fig 2 Systolic brachial artery pressure Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1]	Significance level of difference
Stage 1	Men	$y_x = 135.9 + 37.8x$	$y_x = 116.0 + 31.4x$	—
	Women	$y_x = 165.3 + 61.5x$	$y_x = 117.4 + 39.5x$	—
Stage 2	Men	$y_x = 164.0 + 45.5x$	$\hat{y}_x = 114.4 + 35.8x$	<0.01
	Women	$y_x = 184.1 + 51.5x$	$y_x = 120.8 + 39.5x$	—
Stage 3	Men	$y_x = 160.7 + 47.3x$	$y_x = 114.3 + 36.3x$	<0.05
	Women	$y_x = 172.5 + 65.1x$	$\hat{y}_x = 122.0 + 39.5x$	<0.01

For symbols see Fig 1

[1]) The equations adjusted according to multiple regression functions of the control subjects *Equations (for $V_{O_2\,rest}$ see Fig 1)*

Men $\Delta P_{S_{BA}} / +1.01\ V_{O_2} = 19.3 + 0.346 \times$ Age

Women $P_{S_{BA}\,rest} = 108.2 + 0.456 \times$ Age

TABLE 9 Diastolic brachial artery pressure (mm Hg) at rest

		Mean±standard error $\bar{x} \pm s_{\bar{x}}$	Mean diff from the controls $\bar{d}$	Probability p
Stage 1	Men	83.6±2.3	+10.1	<0.001
	Women	97.5±8.3	+26.4	<0.01
Stage 2	Men	101.0±2.3	+27.5	<0.001
	Women	106.1±3.8	+35.0	<0.001
Stage 3	Men	113.4±4.6	+39.9	<0.001
	Women	97.7±3.6	+26.6	<0.001

TABLE 10 Mean brachial artery pressure (mm Hg) at rest

		Mean±standard error $\bar{x} \pm s_{\bar{x}}$	Mean diff from the controls[1]) $\bar{d}$	Probability p
Stage 1	Men	106.0±2.8	+14.0	<0.001
	Women	127.5±7.6	+35.5	<0.001
Stage 2	Men	129.8±3.1	+35.3	<0.001
	Women	140.4±5.5	+46.1	<0.001
Stage 3	Men	141.9±4.4	+47.0	<0.001
	Women	131.2±6.0	+36.1	<0.001

[1]) Adjusted according to multiple regression functions of the control subjects
Equations Men $\bar{P}_{BArest} = 84.9 + 0.203 \times \text{Age}$ Women $\bar{P}_{BArest} = 80.8 + 0.287 \times \text{Age}$

The pressures of the hypertensive men rose step by step from Stage 1 to Stage 3 The Stage 2 women had the highest mean pressures among the women, and the three female groups did not differ so much from one another as did the male groups

Response to exercise On exercise, the average systolic, diastolic and mean arterial pressure rose in all the hypertensive subjects, both men and women (figs 2–4)

The rise in the systolic and mean arterial pressure in the Stage 1 men did not differ significantly from that in the control men the two groups of subjects differing to about the same extent as in their resting figures The four Stage 1 women showed a higher rise in the systolic and mean arterial pressure than the control subjects but the differences were not significant

The Stage 2 and 3 men showed a significantly higher rise in the systolic and mean arterial pressure on exercise

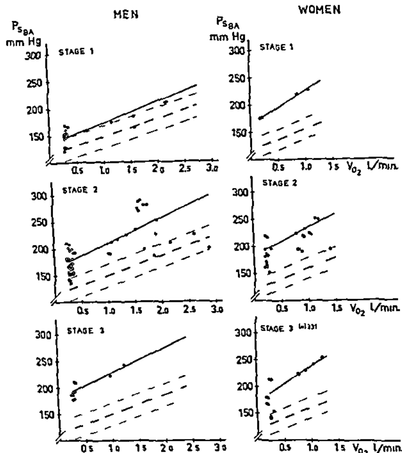

Fig 2 Systolic brachial artery pressure Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1])	Significance level of difference
Stage 1	Men	$y_x = 135\ 9 + 37\ 8\ x$	$\hat{y}_x = 116\ 0 + 31\ 4\ x$	—
	Women	$y_x = 165\ 3 + 61\ 3\ x$	$y_x = 117\ 4 + 39\ 5\ x$	—
Stage 2	Men	$y_x = 164\ 0 + 45\ 5\ x$	$y_x = 114\ 4 + 35\ 8\ x$	<0 01
	Women	$y_x = 184\ 1 + 51\ 5\ x$	$y_x = 1{-}0\ 8 + 39\ 5\ x$	—
Stage 3	Men	$y_x = 180\ 7 + 47\ 3\ x$	$y_x = 114\ 3 + 36\ 3\ x$	<0 05
	Women	$y_x = 1{}^{\circ}2.5 + 65\ 1\ x$	$y_x = 1{-}2\ 0 + 39\ .\ x$	<0 01

For symbols see Fig 1

[1]) The equations adjusted according to multiple regression functions of the control subjects. Equations (for $V_{O_2\ test}$ see Fig 1)

Men $\Delta P_{S_{BA}} / + 1\ 0\ 1\ V_{O_2} = 19\ 3 + 0\ 346 \times Age$

Women $P_{S_{BA}\ test} = 108\ 2 + 0\ 4\ 6 \times Age$

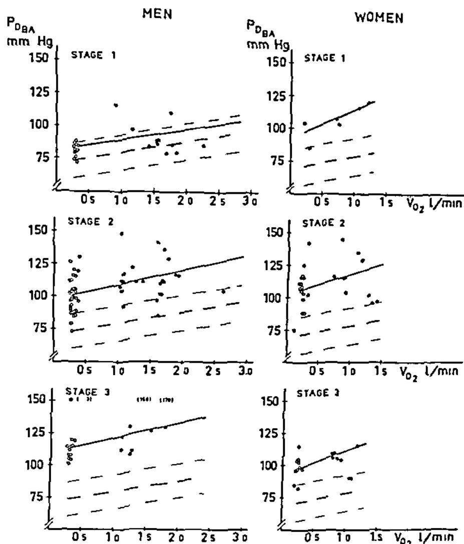

Fig 3 Diastolic brachial artery pressure Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1])	Significance level of difference
Stage 1	Men	$y_x = 81.2 + 8.1x$	$y_x = 71.3 + 8.3x$	—
	Women	$y_x = 93.1 + 21.1x$	$y_x = 69.1 + 9.1x$	—
Stage 2	Men	$\bar{y}_x = 97.[illegible] + 11.4x$	$y_x = 71.2 + 8.3x$	—
	Women	$y_x = 102.5 + 15.7x$	$y_x = 69.1 + 9.1x$	—
Stage 3	Men	$\bar{y}_x = 110.0 + 11.[illegible]x$	$y_x = 71.2 + 8.3x$	—
	Women	$y_x = 93.4 + 18.3x$	$y_x = 69.0 + 9.1x$	< 0.05

For symbols see Fig 1

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[1]) The equations adjusted according to multiple regression functions of the control subjects Equations for V_{O_2} rest see Fig 1

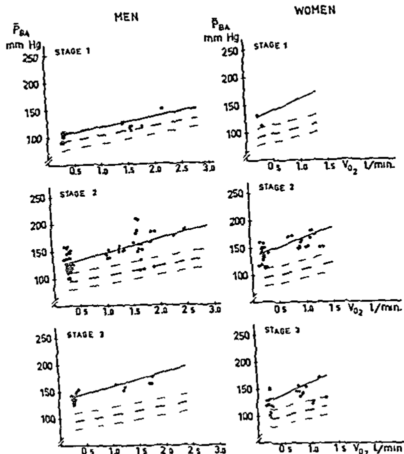

Fig 4 Mean brachial artery pressure Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1])	Significance level of difference
Stage 1	Men	$\hat{y}_x = 100\ 3 + 19\ 1\ x$	$y_x = 8[illegible] + 16\ 5\ x$	—
	Women	$\hat{y}_x = 119\ 0 + 41\ 3\ x$	$y_x = 87\ 3 + 21\ 9\ x$	—
Stage 2	Men	$\hat{y}_x = 1[illegible]2\ 6 + 24\ 9\ x$	$y_x = 89\ 9 + 16\ 5\ x$	<0 001
	Women	$y_x = 132\ 2 + 3[illegible]\ x$	$y_x = 89\ [illegible] + 21\ 9\ x$	<0 0[illegible]
Stage 3	Men	$\hat{y}_x = 134\ 3 + 2[illegible]\ 9\ x$	$y_x = 90\ 3 + 16\ 5\ x$	<0 001
	Women	$y_x = 1[illegible]1\ 6 + 40\ 8\ x$	$y_x = 90\ 1 + 21\ 9\ x$	<0 001

For symbols see Fig 1

[1]) The equations adjusted according to multiple regression functions of the control subjects Equations (for $\dot{V}_{O_2\ rest}$ see Fig 1)

Men $\bar{P}_{BA\ rest} = 84\ 9 + 0\ \ 03 \times$ Age

Women $\bar{P}_{BA\ rest} = 60\ 8 + 0\ [illegible]8 \times$ Age

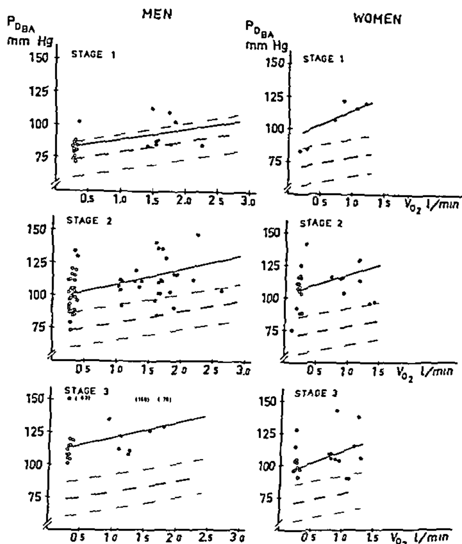

Fig 3 Diastolic brachial artery pressure Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1])	Significance level of difference
Stage 1	Men	$\bar{y}_x = 81\ 2 + 8\ 1\,x$	$y_x = 71\ 3 + 8\ 3\,x$	—
	Women	$y_x = 93\ 1 + 21\ 1\,x$	$y_x = 69\ 1 + 9\ 1\,x$	—
Stage 2	Men	$y_x = 97$ [illegible] $+ 11\ 4\,x$	$y_x = 71\ 2 + 8\ 3\,x$	—
	Women	$y_x = 102$ [illegible] $+ 15\ 7\,x$	$y_x = 69\ 1 + 9\ 1\,x$	—
Stage 3	Men	$y_x = 110\ 0 + 11$ [illegible] x	$y_x = 71\ 2 + 8\ 3\,x$	—
	Women	$\bar{y}_x = 93\ 4 + 18\ 3\,x$	$y_x = 69\ 0 + 9\ 1\,x$	$<0\ 05$

For symbols see *Fig 1*

[1]) The equations adjusted according to multiple regression functions of the control subjects Equations for $\dot{V}_{O_2\ rest}$ see Fig 1

hypertensive patients when they exercise in the supine or sitting position (4 32, 57 73 83 89, 94 137, 146 158) The observations in the present study bear this out On the other hand, Maidorn & Mellerowicz (102) found that the diastolic pressure on auscultation fell in five young subjects with hypertensive regulation disorder when they exercised lying down whereas it rose slightly in their control subjects In Rosenkranz & Drew's (118) subjects with mild essential hypertension the indirectly measured diastolic blood pressure showed practically no change on exercise in the sitting position

The Stage 3 women in the present series showed an almost significantly higher rise in diastolic pressure on exercise than the control women but none of the other groups differed significantly from the control subjects Taylor *et al* (137) found that the diastolic pressure in patients with severe arterial hypertension rose more on exercise in the supine position than in patients less disabled by their disease They did not divide their patients by sex and all except one of the severely disabled patients were men Nor did they compare the observations with those in a control series Varnauskas (146) found no relationship between the rise in diastolic pressure on exercise in the supine position and the functional group or the level of exercise performed but he reported that 10 out of 17 patients studied showed a greater rise in diastolic pressure than did his control subjects

Judging by the reports of other authors and the results of the present study hypertensive subjects react to exercise in the supine or sitting position with a rise in the mean arterial blood pressure (32 73 89 100 137 146) Some authors have noted a greater rise in hypertensive than in normotensive subjects (32, 146) and also a greater rise in severely disabled patients than in ones who are less disabled (137)

Up to now there has been no report of a systematic comparison between hypertensive and normotensive subjects grouped by sex and stage of disease In the Stage 1 men in the present study the mean blood pressure increased on exercise to the same extent relatively, as in the control subjects In the other hypertensive groups, men and women the difference in this value from that in the control subjects widened during exercise

Pulse pressure

At rest All six groups of hypertensive subjects showed a highly significantly greater pulse pressure at rest than the corresponding control groups (table 11) The values for the hypertensive men rose successively with each stage The Stage 2 and 3 women had the same values

Response to exercise The mean pulse pressure increased on exercise in all six groups of hypertensive subjects (fig 5)

The rise was significantly steeper in the Stage 2 men than in the control subjects The mean rise in absolute figures was greatest in the Stage 3 men, but they like the Stage 1 men did not differ significantly from the control men in this respect

than the control men The same was true of the Stage 2 and 3 women for the mean arterial pressure, the differences being almost significant and highly significant in comparison with the control women But only in the Stage 3 women did the systolic pressure rise significantly more than in the control women

Apart from the *Stage 3 women*, the diastolic pressure rose about the same on exercise in the *hypertensive subjects as* in the control *subjects*, the gap between the figures for the two kinds of subjects *remaining* about the same size as *during* rest The Stage 3 women showed an almost significantly higher rise in diastolic pressure on *exercise than the control* women

Comments There was a close correlation between the *resting* arterial pressure and the *WHO class to* which the male *hypertensive* subjects were assigned, but *this was not* true of the women This difference between the men and women *may have* been because of the groups *not being similarly* composed for the two sexes, the female subjects, for example, *tended to have higher* blood pressures on *the average than* the men only 11 of *them having* resting systolic pressures *under 170 as opposed to 30 of* the men *If Stage 3 represents a later* stage in the course of the disease than Stage 2 not another disease the higher values for the Stage 2 women bears out the observation often made that women stand arterial hypertension better than men and that the prognosis for them is more favorable than for men (10 46, 96 129)

All the hypertensive groups of both sexes reacted to exercise with an increase *in the* systolic blood pressure, in agreement *with the observations* of others in *hypertensive subjects* exercising in both the supine and *sitting* position (4, 24, 32, *39, 57, 73, 83, 89,* 94, 137, 146, 158) *In* men at an early stage of the disease, or *Stage 1*, relatively the same rise was observed as in the control men The same was true in the group of young *patients* with "hypertensive regulation disorder' described by Maidorn & Mellerowicz (102)

Nor did the women at Stage 1 or 2 show any significant difference from the control subjects But the Stage 3 women *and the Stage 2* and 3 men showed a significantly steeper rise in systolic blood pressure on exercise than did the control subjects It is not clear whether this agrees with the results in other *series* for most other authors either do not divide their cases by sex or stage of disease, or do not compare them with normotensive control subjects (32, 57 73, 83, 89, 158)

In the series described by Conrad (24) however both the male and female hypertensive subjects showed a consistently lower percentage rise in systolic blood pressure on a step test than did control subjects But all these subjects had been treated and the blood pressure was measured by auscultation Varnauskas (146) found *no correlation between rise* in blood pressure on exercise *in the* supine position and the *functional group* to which the subjects belonged whereas Taylor *et al* (137) noted a much *steeper* rise in systolic pressure in their patients with severe exertional dyspnea

It has been the general observation that the diastolic blood pressure rises in

hypertensive patients when they exercise in the supine or sitting position (4 32, 57 73, 83, 89 94 137 146, 158) The observations in the present study bear this out On the other hand Maidorn & Mellerowicz (102) found that the diastolic pressure on auscultation fell in five young subjects with hypertensive regula tion disorder when they exercised lying down whereas it rose slightly in their control subjects In Rosenkranz & Drews (118) subjects with mild essential hyper tension the indirectly measured diastolic blood pressure showed practically no change on exercise in the sitting position

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Up to now there has been no report of a systematic comparison between hypertensive and normotensive subjects grouped by sex and stage of disease In the Stage 1 men in the present study the mean blood pressure increased on exercise to the same extent relatively as in the control subjects In the other hypertensive groups men and women, the difference in this value from that in the control subjects widened during exercise

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The rise was significantly steeper in the Stage 2 men than in the control subjects The mean rise in absolute figures was greatest in the Stage 3 men, but they like the Stage 1 men did not differ significantly from the control men in this respect

TABLE 11 Pulse pressure (mm Hg) at rest

		Mean ± standard error $\bar{x} \pm s_{\bar{x}}$	Mean diff from the controls $\bar{d}$	Probability p
Stage 1	Men	63.5±2.2	+12.[illegible]	<0.001
	Women	80.[illegible]±4.4	+25.8[1]	<0.001
Stage 2	Men	76.2±2.7	+25.2	<0.001
	Women	89.9±6.6	+32.7[1]	<0.001
Stage 3	Men	81.2±3.9	+30.2	<0.001
	Women	90.1±8.8	+32.9[1]	<0.001

[1]) Adjusted according to multiple regression functions of the control subjects
Equation $PP_{rest} = 42.1 + 0.321 \times Age$

The Stage 3 women showed an almost *significantly greater rise in pulse pressure* on exercise than the control women. The other hypertensive women did not differ significantly from the control women in this respect.

Comments As far as known, there has been no previous study on the response of the pulse pressure to exercise in patients with established arterial hypertension. On the pulse pressure during or after exercise in patients with early hypertension, the literature contains only a few reports. Thus König *et al* (94) and Maidorn & Mellerowicz (102) found that patients with "hypertensive regulation disorder" had a higher pulse pressure than control subjects both at rest and during exercise in the supine position. In another investigation, young persons with a family disposition to arterial hypertension or coronary disease had a greater rise in pulse pressure after exercise than other subjects (140).

In the present study, all the hypertensive subjects of both sexes showed a general tendency to a greater average rise in pulse pressure on exercise than did the control subjects. The values within the separate groups varied a great deal however; only the Stage 2 men and Stage 3 women differed to a noteworthy extent from the control subjects in this respect, the differences being significant and almost significant, respectively.

Cardiac output

At rest At rest the Stage 1 men had a significantly higher cardiac output on the average than the control subjects (table 12). The hypertensive men at Stage 2 had the same average cardiac output as the control men. The average output in the Stage 3 men was lower than that in the control men, the difference being almost significant.

The hypertensive women also showed a tendency to a progressive decline in cardiac output with increasing severity of disease (table 12), but there were no significant differences between the three hypertensive female groups or between them and the control women.

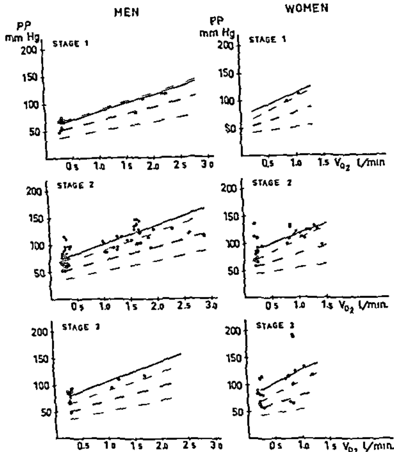

Fig 5 Pulse pressure Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1])	Significance level of difference
Stage 1	Men	$\hat{y}_x = 54\ 7 + 29\ 8\ x$	$y_x = 44\ 7 + 23\ [illegible]\ x$	—
	Women	$\hat{y}_x = 72\ 2 + 40\ 2\ x$	$\hat{y}_x = 48\ 2 + 30\ 4\ x$	—
Stage 2	Men	$\hat{y}_x = 66\ 3 + 34\ 1\ x$	$\hat{y}_x = 43\ 6 + 26\ 4\ x$	<0 01
	Women	$\hat{y}_x = 81\ 7 + 35\ 8\ x$	$y_x = 50\ 4 + 30\ 4\ x$	—
Stage 3	Men	$y_x = 70\ 7 + 35\ 6\ x$	$\hat{y}_x = 43\ [illegible] + 26\ 8\ x$	—
	Women	$\hat{y}_x = 79\ 1 + 46\ 7\ x$	$\hat{y}_x = 50\ 2 + 30\ 4\ x$	<0 05

For symbols see Fig 1

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[1]) The equations adjusted according to multiple regression functions of the control subjects. Equations (for $\dot{V}_{O_2\ rest}$ see Fig 1)

Men. $\Delta PP/\Delta + 1\ 0\ \dot{V}_{O_2} = 14\ 5 + 0\ 51 \times$ Age

Women $PP_{rest} = 42.1 + 0\ 3\ 1 \times$ Age

TABLE 11. Pulse pressure (mm Hg) at rest

		Mean ± standard error $\bar{x} \pm s_{\bar{x}}$	Mean diff. from the control $\bar{d}$	Probability p
Stage 1	Men	[illegible]	[illegible]	<0.001
	Women	[illegible]	[illegible] †)	<0.001
Stage 2	Men	[illegible]	[illegible]	<0.001
	Women	[illegible]	[illegible] †)	<0.001
Stage 3	Men	[illegible]	+30.[illegible]	<0.001
	Women	90 ± [illegible]	[illegible] †)	<0.001

†) Adjusted according to multiple regression function in the control subjects.
Control: PP_{rest} = [illegible] age

The Stage 3 women showed an almost significantly greater rise in pulse pressure on exercise than the control women. The other hypertensive women did not differ significantly from the control women in this respect.

Comments. As far as known, there has been no previous study on the response of the pulse pressure to exercise in women with established arterial hypertension. On the pulse pressure during or after exercise in patients with early hypertension the literature contains only a few reports. Thus Kung et al. ([illegible]) and Mathers & Muller-[illegible] (102) found that patients with "hypertensive regulation disorder" had a higher pulse pressure than control subjects both at rest and during exercise in the supine position. In another investigation young persons with a family disposition to essential hypertension or coronary disease had a greater rise in pulse pressure after exercise than other subjects (140).

In the present study all the hypertensive subjects of both sexes showed a general tendency to a greater average rise in pulse pressure on exercise than did the control subjects. The values within the separate groups varied a great deal, however; only the Stage 2 men and Stage 3 women differed to a noteworthy extent from the control subjects in this respect, the differences being significant and almost significant respectively.

Cardiac output

Men. At rest the Stage 1 men had a significantly higher cardiac output on the average than the control subjects (Table 12). The hypertensive men at Stage 2 had the same average cardiac output as the control men. The average output in the Stage 3 men was lower than that in the control men, the difference being almost significant.

The hypertensive women also showed a tendency to a progressive decline in cardiac output with increasing severity of disease (Table 12), but there were no significant differences between the three hypertensive female groups or between them and the control women.

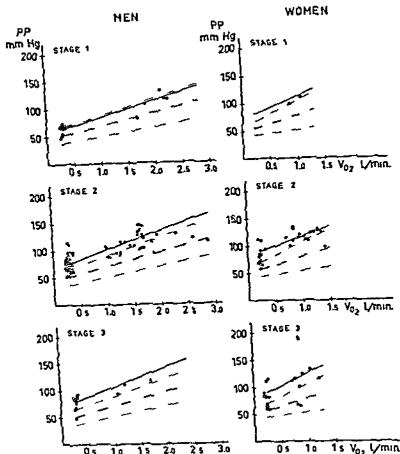

Fig 5 Pulse pressure Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1]	Significance level of difference
Stage 1	Men	$y_x = 54.7 + 29.8\,x$	$y_x = 44.7 + 23.2\,x$	—
	Women	$y_x = 72.2 + 40.2\,x$	$y_x = 48.2 + 30.4\,x$	—
Stage 2	Men	$y_x = 66.3 + 34.1\,x$	$y_x = 43.6 + 26.4\,x$	<0.01
	Women	$y_x = 81.7 + 35.8\,x$	$y_x = 50.4 + 30.4\,x$	—
Stage 3	Men	$y_x = 70.7 + 35.8\,x$	$y_x = 43.5 + 26.8\,x$	—
	Women	$y_x = 79.1 + 46.7\,x$	$y_x = 50.2 + 30.4\,x$	<0.05

For symbols see Fig 1

[1] The equations adjusted according to multiple regression functions of the control subjects Equations (for $V_{O_2\,rest}$ see Fig 1)

Men. $PP_{rest} + 1.01\,V_{O_2} = 14.5 + 0.251 \times$ Age

Women $PP_{rest} = 42.1 + 0.321 \times$ Age

TABLE 12 Cardiac output (l/min.) at rest

		Mean ± standard error $\bar{x} \pm s_{\bar{x}}$	Mean diff from the controls d	Probability p
Stage 1	Men	7.19 ± 0.30	−1.16¹)	<0.01
	Women	5.63 ± 0.13	+0.35	—
Stage 2	Men	5.88 ± 0.19	−0.03¹)	—
	Women	5.21 ± 0.20	−0.0	—
Stage 3	Men	5.35 ± 0.21	−0.5 ¹)	<0.05
	Women	4.96 ± 0.27	−0.32	—

¹) Adjusted according to multiple regression functions of the control subjects
Equation $Q_{rest} = 2.60 - 0.0?57 \times Age + 2.352 \times BSA$

Response to exercise The cardiac output rose less with a rise in oxygen consumption in the hypertensive men and women at Stage 1 than in the corresponding control groups, the differences being almost and highly significant, respectively (fig 6) The subjects at Stage 2 and 3 did not differ from the control subjects in this respect

Comments The observation that the resting cardiac output in the hypertensive men at Stage 1 was significantly high agrees with the observations made during recent years in patients with early arterial hypertension examined in the supine position (11 22 33 45 94 131 154) The four Stage 1 women did not differ from the control women in this respect but they were too few to say whether or not this was because of a real sex difference in resting cardiac output The literature is of no help here because no former authors have studied this feature in subjects divided by sex

It is the general opinion (11 18 21, 45 120, 137, 146 152) that the resting cardiac output is normal in subjects with established arterial hypertension, and the present results are in agreement with this That patients with advanced arterial hypertension designated as Stage 3 here have lower outputs at rest than normotensive subjects has been noted by many authors (11 22 58 75 78 120 137 146 152)

So far no one has reported having measured the cardiac output of hypertensive subjects during exercise in the sitting position Studies of normotensive subjects (13 68) have shown that the output increases to practically the same extent relatively whether the subjects exercise lying down or sitting The same does not need to apply to subjects with arterial hypertension however Thus it has been shown that the plasma volume in hypertensive subjects decreases more than normal when they change from the supine to the standing position (36) Accordingly it is not right directly to compare the present results with those made in earlier investigations of hypertensive subjects in the supine position

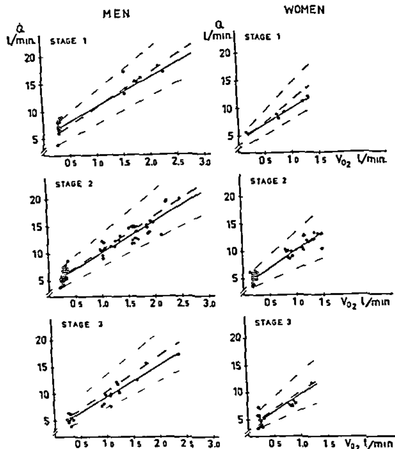

Fig. 6. Cardiac output. Response to exercise. Regression equations.

		Hypertensive subjects	Control subjects[1]	Significance level of difference
Stage I	Men	$\hat{y}_x = 5.6[illegible] + 5.13\,x$	$\hat{y}_x = 4.33 + 6.[illegible]9\,x$	<0.05
	Women	$y_x = 4.51 + 5.43\,x$	$\hat{y}_x = 3.65 + 7.60\,x$	<0.001
Stage 2	Men	$y_x = 4.18 + 5.83\,x$	$y_x = 4.14 + 6.29\,x$	–
	Women	$y_x = 3.[illegible]3 + 6.42\,x$	$y_x = 3.88 + 6.[illegible]3\,x$	–
Stage 3	Men	$y_x = 3.64 + 5.[illegible]3\,x$	$y_x = 4.08 + 6.[illegible]9\,x$	–
	Women	$y_x = 3.48 + 6.2[illegible]\,x$	$y_x = 3.81 + 6.43\,x$	–

For symbols see Fig. 1.

[1] The equations adjusted according to multiple regression functions of the control subjects. Equations. (for $\dot{V}_{O_2\,rest}$ see Fig. 1)
Men $Q_{rest} = 2.60 - 0.0[illegible]8 \times Age + 2.382 \times BSA$.
Women $\Delta Q/[illegible]\,\dot{V}_{O_2} = -1.[illegible]5 + 0.193 \times Height - 0.140 \times Weight$

TABLE 12 Cardiac output (l/min) at rest

		Mean ± standard error $x \pm s_{\bar{x}}$	Mean diff from the controls $\bar{d}$	Probability p
Stage 1	Men	7 19±0 39	+1 16[1])	<0 01
	Women	5 63±0 18	+0 35	–
Stage 2	Men	5 88±0 19	−0 03[1])	–
	Women	5 21±0 20	−0 07	–
Stage 3	Men	5 32±0 21	−0 52[1])	<0 05
	Women	4 96±0 27	−0 32	–

[1]) Adjusted according to multiple regression functions of the control *subjects*
Equation $Q_{rest} = 2\ 60 - 0\ 0287 \times Age + 2\ 382 \times BSA$

Response to exercise The cardiac output rose less with a rise in oxygen consumption in the hypertensive men and women at Stage 1 than in the corresponding control groups, the differences being almost and highly significant, respectively (fig 6) The subjects at Stage 2 and 3 did not differ from the control subjects in this respect

Comments The observation that the resting cardiac output in the hypertensive men at Stage 1 was significantly high agrees with the observations made during recent years in patients with early arterial hypertension examined in the supine *position* (*11*, *22* *33* *45*, *94*, 131 154) The four Stage 1 women did not differ from the control women in this respect, but they were too few to say whether or not this was because of a real sex difference in resting cardiac output The literature is of no help here, because no former authors have studied this feature in subjects divided by sex

It is the *general opinion* (11, 18, 21, 45, 120, 137, 146, 152) that the resting cardiac output is normal in subjects with established arterial hypertension and the present results are in agreement with this That patients with advanced arterial hypertension, designated as Stage 3 here have lower outputs at rest than normotensive subjects has been noted by many authors (*11*, *22* *58* *75* *78*, 120, 137, 146, 152)

So far no one has reported having measured the cardiac output of hypertensive subjects during exercise in the sitting position Studies of normotensive subjects (13, 68) have shown that the output increases to practically the same extent, relatively, whether the subjects *exercise lying down or sitting* The same does not need to apply to subjects with arterial *hypertension, however* Thus it has been shown that the plasma volume in hypertensive subjects decreases more than normal when they change from the supine to the standing position (36) Accordingly it is not right directly to compare the present results with those made in earlier investigations of hypertensive subjects in the supine position

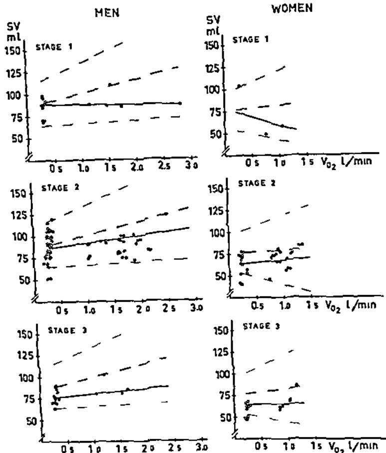

Fig 7 Stroke volume Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1]	Significance level of difference
Stage 1	Men	$y_x = 88.7 - 0.9x$	$y_x = 8[illegible].9 + 14.7x$	<0.01
	Women	$y_x = 78.9 - 19.8x$	$y_x = 73.8 + 6.6x$	<0.01
Stage 2	Men	$y_x = 84.5 + [illegible].2x$	$y_x = 88.3 + 14.7x$	<0.05
	Women	$y_x = 62.9 + 4.9x$	$y_x = 76.6 + 2.7x$	–
Stage 3	Men	$y_x = 7[illegible].0 + [illegible]x$	$y_x = 8[illegible].0 + 14 [illegible]x$	<0.05
	Women	$y_x = 64.8 - 0.03x$	$y_x = 7[illegible].4 + 7.9x$	–

For symbols see Fig 1

---

[1] The equations adjusted according to multiple regression functions of the control subjects Equations. (for $\dot{V}_{O_2\ rest}$ see Fig 1)
Men $SV_{rest} = 4[illegible].7 - 0.3[illegible]6 \times$ Age $+ [illegible] \times$ BSA,
Women $\Delta SV/ + 1.0 l\ \dot{V}_{O_2} = -30$ [illegible] $\times$ Height

TABLE 13 *Stroke volume (ml) at rest*

		Mean ± standard error $\bar{x} \pm s_{\bar{x}}$	Mean diff from the controls $\bar{d}$	Probability p
Stage 1	Men	88.4 ± 5.2	− 1.5[1]	—
	Women	74.8 ± 10.2	− 2.4	—
Stage 2	Men	86.6 ± 2.9	− 3.8[1]	—
	Women	64.0 ± 3.2	−13.2	<0.01
Stage 3	Men	76.5 ± 2.2	−12.6[1]	<0.001
	Women	64.8 ± 4.0	−12.4	<0.01

[1]) Adjusted according to multiple regression functions of the control subjects
Equation $SV_{rest} = 4.7 - 0.376 \times Age + 52.82 \times BSA$

Konig *et al* (94) noted a higher than normal cardiac output both at rest and on exercise in the supine position in four patients with "hypertensive regulation disorder" In the present study the hypertensive men with a high resting cardiac output showed a lower rise in output than the control subjects on exercise in the sitting position, the difference being almost significant The same pattern was seen for the women with early arterial hypertension in this study

The hypertensive men and women at Stage 2 showed the same response of cardiac output to exercise as the control subjects, which agrees with the observations of other authors in patients with established hypertension in the supine position (100, 137, 146) Nor did the subjects with advanced hypertension in the present study differ from the controls in this respect Other investigators (76 100, 125, 137) have noted that patients with latent or previous heart failure show a subnormal increase in cardiac output on exercise in the supine position Although 8 of the present hypertensive subjects had a heart volume of more than 500 ml per square meter of body surface, the series is not sufficiently representative to permit comparison with the subjects of other authors

Stroke volume

At rest The hypertensive men at Stage 1 and 2 did not differ significantly from the control men in mean stroke volume at rest (table 13) The Stage 3 men had a highly significantly lower stroke volume

The Stage 2 and 3 women had a significantly lower stroke volume than the control women (table 13) The Stage 1 women did not differ significantly from the control women

Response to exercise The Stage 1 men showed no increase in stroke volume on exercise, differing significantly from the control men in this respect (fig 7) The Stage 2 and 3 men showed an almost significantly smaller rise in stroke volume than the control subjects

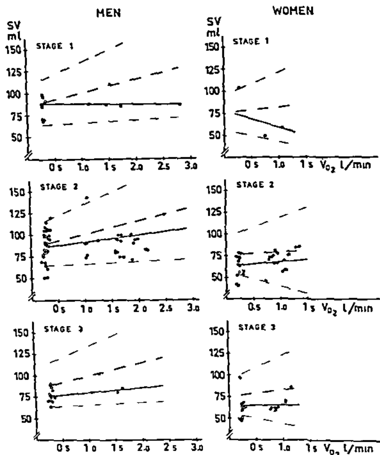

Fig 7 Stroke volume Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1])	Significance level of difference
Stage 1	Men	$y_x = 88\ 7 - 0\ 9x$	$y_x = 83\ 0 + 14\ 7x$	<0 01
	Women	$y_x = 78\ 9 - 19\ 8x$	$y_x = 75\ 8 + 6\ 6x$	<0 01
Stage 2	Men	$y_x = 84 + [illegible]\ 2x$	$y_x = 86\ 3 + 14\ x$	<0 05
	Women	$y_x = 62\ 9 + 4\ 9x$	$y_x = 76\ 6 + 2\ 7x$	—
Stage 3	Men	$y_x = 75\ 0 + 5\ 2x$	$y_x = 85\ 0 + 14\ 7x$	<0 05
	Women	$\hat{y}_x = 64\ 8 + 0\ 03x$	$y_x = 75\ 4 + 7\ 9x$	—

For symbols see Fig 1

[1]) The equations adjusted according to multiple regression functions of the control subjects

Equations (for $V_{O_2\ rest}$ see Fig 1)

Men $SV_{rest} = 4\ 7 - 0\ 3\ 6 \times Age + 52\ 82 \times BSA$

Women $\Delta SV / +1\ 0\ l\ V_{O_2} = -30\ 7\ 1 - 1\ 9\ 7 \times Height$

TABLE 13 Stroke volume (ml) at rest

		Mean ± standard error $\bar{x} \pm s_{\bar{x}}$	Mean diff from the controls $\bar{d}$	Probability p
Stage 1	Men	88.4 ± 5.2	− 1.5[1]	—
	Women	74.8 ± 10.2	− 2.4	—
Stage 2	Men	86.6 ± 2.9	− 3.5[1]	—
	Women	64.0 ± 3.2	−13.2	<0.01
Stage 3	Men	76.5 ± 2.2	−12.6[1]	<0.001
	Women	64.8 ± 4.0	−12.4	<0.01

[1]) Adjusted according to multiple regression functions of the control subjects
Equation $SV_{rest} = 4.7 - 0.376 \times Age + 52.82 \times BSA$

Konig *et al* (94) noted a higher than normal cardiac output both at rest and on exercise in the supine position in four patients with "hypertensive regulation disorder" In the present study the hypertensive men with a high resting cardiac output showed a lower rise in output than the control subjects on exercise in the sitting position, the difference being almost significant The same pattern was seen for the women with early arterial hypertension in this study

The hypertensive men and women at Stage 2 showed the same response of cardiac output to exercise as the control subjects, which agrees with the observations of other authors in patients with established hypertension in the supine position (100, 137, 146) Nor did the subjects with advanced hypertension in the present study differ from the controls in this respect Other investigators (76 100, 125, 137) have noted that patients with latent or previous heart failure show a subnormal increase in cardiac output on exercise in the supine position Although 8 of the present hypertensive subjects had a heart volume of more than 500 ml per square meter of body surface, the series is not sufficiently representative to permit comparison with the subjects of other authors

Stroke volume

At rest The hypertensive men at Stage 1 and 2 did not differ significantly from the control men in mean stroke volume at rest (table 13) The Stage 3 men had a highly significantly lower stroke volume

The Stage 2 and 3 women had a significantly lower stroke volume than the control women (table 13) The Stage 1 women did not differ significantly from the control women

Response to exercise The Stage 1 men showed no increase in stroke volume on exercise differing significantly from the control men in this respect (fig 7) The Stage 2 and 3 men showed an almost significantly smaller rise in stroke volume than the control subjects

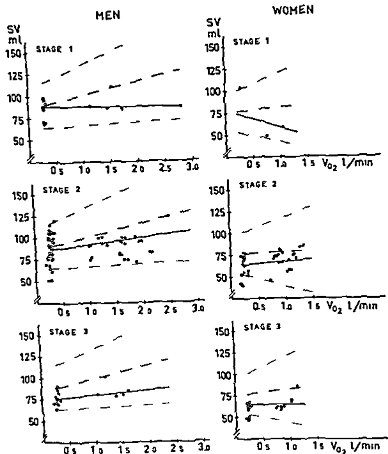

Fig 7 Stroke volume Re-ponse to exercise Regression equations

		Hypertensive subjects	Control subjects[1])	Significance level of difference
Stage 1	Men	$y_x = 88\ 7 - \ 0\ 9x$	$y_x = 85\ 9 + 14\ 7x$	< 0 01
	Women	$y_x = 78\ 9 - 19\ 8x$	$y_x =$ [illegible] $8 + \ 6\ 6x$	< 0 01
Stage 2	Men	$y_x = 84\ 5 -$ [illegible] $2x$	$y_x = 86\ 3 + 14\ 7x$	< 0 05
	Women	$y_x = 62\ 9 + \ 4\ 9x$	$y_x =$ [illegible]$6\ 6 + \ 2$ [illegible] x	—
Stage 3	Men	$y_x =$ [illegible] $0 +$ [illegible] $2x$	$y_x = 8$[illegible]$\ 0 + 14\ 7x$	< 0 05
	Women	$y_x = 64\ 8 + \ 0\ 03x$	$y_x = 75\ 4 + \ 7\ 9x$	—

For symbols see Fig 1

[1]) The equations adjusted according to multiple regression functions of the control subjects Equations (for $V_{O_2\,rest}$ see Fig 1)
Men SV_{rest} = 4 [illegible] − 0 3 6 × Age + [illegible]2 82 × BSA
Women ΔSV/+1 01 V_{O_2} = −307 1 + 1 927 × Height

The stroke volume fell on exercise in the hypertensive women at Stage 1 and remained the same in the Stage 3 women (fig 7), but only the Stage 1 women differed significantly from the control women in response of this volume to exercise In the Stage 2 women, however, the stroke volume increased to the same extent on exercise as in the control subjects, the gap between the two kinds of subjects during the resting state remaining the same during exercise

Comments In normotensive subjects, the stroke volume is much lower in the upright than the supine position (13, 68, 143) Whether this is also true of hyper tensive subjects is not clear from the literature, because most of it deals only with patients examined in the supine position In some reports nothing is said about the subjects' position (58, 78) The study of Onesti *et al* (111) appears to be the only one in which the effect of the body position on the stroke volume in arterial hypertension has been exa mined, they found that the average volume in 8 patients with essential hyper tension dropped about 20 per cent when they were tilted to an angle of 45 degrees This is consistent with the figures ob tained by Granath *et al* (68) from healthy old men, and of Ward *et al* (148) from healthy men and women of 18 to 51 years of age on a change from the supine to the sitting position Bevegård *et al* (13) noted an even larger drop in healthy young men

In the present study, the Stage 1 subjects, both men and women, gave the same values for resting stroke volume as the control subjects The reports in the literature do not agree on the stroke volume in the supine position in patients with early hypertension In agreement with the present results, Varnauskas (146) and Glazer (58) found no note worthy differences from normal, but others (11, 45, 154) say that the stroke volume in these cases is raised Eich *et al* (33) found that the stroke volume was high in patients with labile hypertension who had a high cardiac output

On the other hand, most of the earlier authors seem to be agreed that the resting stroke volume in subjects with established hypertension without heart failure is normal (45 58, 78, 100, 137, 146), and the observations in the Stage 2 men in this report agree with this The Stage 2 women, on the other hand, had a significantly low stroke volume The earlier authors did not divide their subjects by sex and so there are no figures with which to compare the results in the Stage 2 women

The significant drop in the resting stroke volume in the Stage 3 subjects tallies with the opinion of several authors that advanced stages of hypertensive disease are characterized by a reduced stroke volume (58 78 100, 137, 146)

On exercise, the Stage 1 men and women showed a tendency to a drop in stroke volume This does not agree with Konig *et al* s (94) observation that the volume in four patients with hypertensive regu lation disorder increased greatly during exercise in the supine position and more than in control subjects

Except for the Stage 2 women the Stage 2 and 3 subjects showed a tendency to less rise in the stroke volume on exercise than the control subjects or no

TABLE 14 Systemic vascular resistance (units) at rest

		Mean ± standard error $x \pm s_{\bar{x}}$	Mean diff from the controls[1] $\bar{d}$	Probability p
Stage 1	Men	15 34±0 90	− 0 34	—
	Women	22 65±1 06	+ 4 61	<0 001
Stage 2	Men	22 86±0 88	+ 6 54	<0 001
	Women	27 90±1 83	+ 8 86	<0 001
Stage 3	Men	27 11±1 17	+10 53	<0 001
	Women	27 59±1 97	+ 8 1	<0 001

[1] Adjusted according to multiple regression functions of the control subjects

Equations Men. SVR_{rest} = 24 86+0 106 × Age − 6 918 × BSA

Women SVR_{rest} = 13 16+0 125 × Age

rise at all The reports in the literature vary on the response to exercise of the stroke volume in hypertensive subjects in the supine position Taylor *et al* (137) noted a moderate rise or a small one like that in normotensive subjects irrespective of the severity of the disease Varnauskas (146) observed the same Lewis *et al* (100) found that the stroke volume did not rise in patients with a high pulmonary capillary venous pressure at rest but that it rose to a normal extent in ones without an increased pressure in the lesser circulation Harvey *et al* (73) on the other hand noted a rise in stroke volume whether or not the patient showed signs of left heart failure

Systemic vascular resistance

At rest The resting systemic vascular resistance was the same in the hypertensive men at Stage 1 as in the control subjects (table 14) but it was highly significantly elevated in the Stage 2 and 3 men The Stage 3 men had the highest average value

All three groups of hypertensive women had highly significantly elevated values for resting systemic resistance (table 14) The Stage 2 women had the highest average value

Response to exercise The change in the systemic resistance on exercise is shown in figure 8 where the mean arterial pressure is plotted against the rise in cardiac output the slope of the regression line showing the change in the resistance with an increase in the cardiac output

All the hypertensive subjects showed a lowered systemic vascular resistance during exercise The mean arterial pressure rose much more in relation to cardiac output in the hypertensive men at Stage 2 and 3 than in the control subjects the differences being highly significant and significant respectively The Stage 1 men showed the same tendency but not a significant difference from the control subjects

All three groups of hypertensive women showed a steep rise in mean arterial

The stroke volume fell on exercise in the hypertensive women at Stage 1 and remained the same in the Stage 3 women (fig 7) but only the Stage 1 women differed significantly from the control women in response of this volume to exercise In the Stage 2 women, however, the stroke volume increased to the same extent on exercise as in the control subjects the gap between the two kinds of subjects during the resting state remaining the same during exercise

Comments In normotensive subjects, the stroke volume is much lower in the upright than the supine position (13, 68, 143) Whether this is also true of hypertensive subjects is not clear from the literature, because most of it deals only with patients examined in the supine position In some reports nothing is said about the subjects' position (58 78) The study of Onesti *et al* (111) appears to be the only one in which the effect of the body position on the stroke volume in arterial hypertension has been examined, they found that the average volume in 8 patients with essential hypertension dropped about 20 per cent when they were tilted to an angle of 45 degrees This is consistent with the figures obtained by Granath *et al* (68) from healthy old men, and of Ward *et al* (148) from healthy men and women of 18 to 51 years of age on a change from the supine to the sitting position Bevegård *et al* (13) noted an even larger drop in healthy young men

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On the other hand, most of the earlier authors seem to be agreed that the resting stroke volume in subjects with established hypertension without heart failure is normal (45, 58, 78, 100, 137, 146), and the observations in the Stage 2 men in this report agree with this The Stage 2 women on the other hand, had a significantly low stroke volume The earlier authors did not divide their subjects by sex, and so there are no figures with which to compare the result in the Stage 2 women

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On exercise, the Stage 1 men and women showed a tendency to a drop in stroke volume This does not agree with König *et al*'s (94) observation that the volume in four patients with hypertensive regulation disorder increased greatly during exercise in the supine position and more than in control subjects

Except for the Stage 2 women the Stage 2 and 3 subjects showed a tendency to less rise in the stroke volume on exercise than the control subjects or no

TABLE 15 Systemic vascular conductance (units) at rest

		Mean ± standard error $x \pm s_x$	Mean diff from the controls[1] $\bar{d}$	Probability p
Stage 1	Men	67.8 ± 3.3	+ 2.0	–
	Women	44.5 ± 1.9	−12.8	<0.001
Stage 2	Men	46.0 ± 1.7	−17.0	<0.001
	Women	38.3 ± 2.4	−16.1	<0.001
Stage 3	Men	37.8 ± 1.7	−24.1	<0.001
	Women	39.1 ± 3.0	−14.1	<0.001

[1]) Adjusted according to multiple regression functions of the control subjects

Equations Men. $SVC_{rest} = 27.3 - 0.460 \times Age + 29.29 \times BSA$

Women $SVC_{rest} = 71.7 - 0.3\ 0 \times Age$

pressure in relation to rise in cardiac output (fig 8) the Stage 2 women showing a significant difference from the control women in this respect and the Stage 3 women a highly significant difference

Systemic vascular conductance

At rest The average value for systemic vascular conductance in the Stage 1 men at rest was the same as that of the control subjects (table 15) All the other hypertensive groups of both sexes had values highly significantly below those of the corresponding control groups

Response to exercise The systemic vascular conductance did not rise as high on exercise in any of the hypertensive groups of either sex as in the control subjects the differences being highly significant for all six groups (fig 9)

Comments The lack of a difference between the Stage 1 and control men in vascular resistance and conductance in the systemic circulation at rest agrees with the observation of other authors (11, 33, 45, 58, 152, 154) that patients with early arterial hypertension often show no signs of alteration in the resting systemic vascular resistance in comparison with normotensive subjects

Unlike the Stage 1 men, the Stage 1 women had higher resting values for vascular resistance and lower for conductance than their control group both differences being highly significant But there were too few cases in this group and as there are no comparable cases reported in the literature, it is impossible to draw any conclusions on a sex difference

The highly significant differences Stages 2 and 3 showed from the control subjects in systemic resistance and conductance at rest agree with the observations of other authors in patients with established arterial hypertension (11 21 45 58 75 78 120 137, 146 152) The present study gives no information on the possibility of local

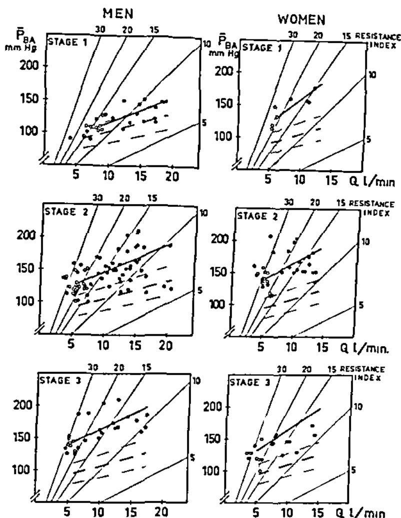

Fig 8 Mean brachial artery pressure/cardiac output Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1])	Significance level of difference
Stage 1	Men	$y_x = 78.0 + 3.9\,x$	$y_x = 75.1 + 2.8\,x$	—
	Women	$y_x = 83.6 + 7.8\,x$	$y_x = 75.6 + 3.1\,x$	—
Stage 2	Men	$y_x = 104.5 + 4.3\,x$	$y_x = 78.0 + 2.8\,x$	<0.001
	Women	$y_x = 111.7 + 5.[illegible]\,x$	$\bar{y}_x = 77.9 + 3.1\,x$	<0.01
Stage 3	Men	$\bar{y}_x = 116.9 + 4.7\,x$	$y_x = 78.5 + 2.8\,x$	<0.01
	Women	$y_x = 98.5 + 6.6\,x$	$y_x = 78.7 + 3.1\,x$	<0.001

For symbols see Fig 1

---

[1]) *The equations adjusted according to multiple regression functions of the control subjects*
Equations
Men $\bar{P}_{BA\,rest} = 84.9 + 0.203 \times \text{Age}$ $Q_{rest} = 2.60 - 0.0287 \times \text{Age} + 2.382 \times \text{BSA}$
Women $\bar{P}_{BA\,rest} = 80.8 + 0.28[illegible] \times \text{Age}$

differences in the systemic vascular resistance in arterial hypertension It is assumed however that the vascular resistance is raised the same throughout the organism with the exception of the kidneys in which the flow of blood is slightly reduced (51 146, 147) Recently however Brod *et al* (21) have produced evidence that patients with uncomplicated essential hypertension show a greater flow of blood through the muscles of their forearms than do normotensive persons, indicating that the vascular resistance *is lowered in this section of the vascular* system

The reports in the literature on the response to exercise of the systemic vascular resistance in subjects with arterial *hypertension are both few in number* and contradictory in results Moreover all the investigations so far on this condition have been done with the subjects in the supine position Taylor *et al* (137) found that the systemic vascular resistance in all their patients regardless of degree of disability dropped to a normal extent on exercise Var nauskas (146) patients especially the more disabled ones showed a lowering in resistance much the same as his control subjects, but several showed a rise in the resistance on exercise Lewis *et al* (100) observed a normal fall in resistance in decompensated patients with a normal pulmonary capillary venous pressure at rest

On exercise, the systemic vascular resistance *fell* and the vascular conductance rose in all the present subjects The conductance rose less however, in *the hypertensive than in the control* subjects This was seen already in the men with early arterial hypertension, who at rest showed the same values for conductance as the control subjects *but on exercise a highly significantly* lower rise

Arteriovenous oxygen difference

At rest The resting arteriovenous oxygen difference in the hypertensive men showed a tendency to widen with the severity of the disease (table 16) Thus the mean difference for the Stage I men was no

TABLE 16 Arteriovenous oxygen difference (ml/l) at rest

		Mean ± standard error $x \pm s_x$	Mean diff from the controls $\bar{d}$	Probability p
Stage 1	Men	43 1 ± 2 7	− 2 4	—
	Women	37 0 ± 5 9	− 7 5[1])	—
Stage 2	Men	50 5 ± 1 8	+ 5 0	<0 001
	Women	44 9 ± 2 2	− 2 0[1])	—
Stage 3	Men	56 4 ± 3 0	+10 9	<0 001
	Women	49 4 ± 2	+ 1 6[1])	—

[1]) Adjusted according to multiple regression functions of the *control subjects*
Equation $(a-v)_{O_2\ rest} = 32\ 6 + 0\ 304 \times Age$

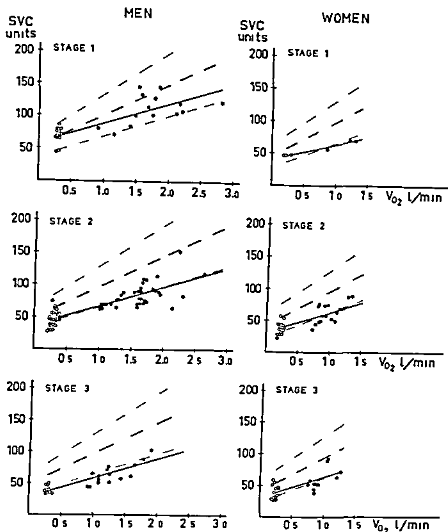

Fig 9 Systemic vascular conductance Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1]	Significance level of difference
Stage 1	Men	$\bar{y}_x = 58.9 + 30.0x$	$y_x = 52.9 + 47.9x$	<0.001
	Women	$y_x = 39.7 + 23.0x$	$y_x = 45.8 + 53.3x$	<0.001
Stage 2	Men	$y_x = 37.3 + 29.8x$	$y_x = 49.4 + 47.9x$	<0.001
	Women	$y_x = 31.2 + 30.8x$	$\bar{y}_x = 42.5 + 53.3x$	<0.001
Stage 3	Men	$y_x = 29.4 + 28.7x$	$y_x = 48.4 + 47.9x$	<0.001
	Women	$\bar{y}_x = 31.9 + 30.5x$	$y_x = 41.0 + 53.3x$	<0.001

For symbols see Fig 1

[1]) The equations adjusted according to multiple regression functions of the control subjects

Equations (for V_{O_2} rest, see Fig 1)

Men $SVC_{rest} = 27.3 - 0.460 \times Age + 29.29 \times BSA$

Women $SVC_{rest} = 71.7 - 0.3?0 \times Age$

different from that for the control men while that for Stage 2 and 3 men was wider than that for the control men, the differences being highly significant

The hypertensive women showed the same tendency to a successive widening of the difference from Stage 1 to 3 (table 16) but no group differed significantly from the control women in this respect

Response to exercise In all six groups of hypertensive subjects both men and women the arteriovenous oxygen difference rose during exercise (fig 10) but none of the groups differed significantly from the control subjects in this respect

Comments The arteriovenous oxygen difference at rest in the supine position is said to be almost the same in hypertensive subjects showing no signs of cardiac decompensation as in control subjects (137 146) In the male hypertensive subjects studied here this was true only of Stage 1 in which the average value lay slightly below that of the control subjects this tallies with the observations of Werko & Lagerlof (152) and Konig *et al* (94) in subjects with early arterial hypertension The Stage 2 men on the other hand had a wider arteriovenous oxygen difference than the control men the difference being highly significant Rowe *et al* (120) also observed that the difference was greater for Smithwick grade I and 2 patients without signs of heart failure than for normotensive subjects

The highly significantly wider resting arteriovenous oxygen difference for the Stage 3 men agrees with the observations of other authors in advanced hypertension (100 120 137 146 152)

None of the groups of hypertensive women differed significantly from the normotensive subjects in the arteriovenous oxygen difference at rest There are no figures in the literature with which to compare the ones from these women Like the men they showed a tendency to a successive widening of the difference with increasing severity of disease

All the studies so far on the effect of exercise on the arteriovenous oxygen difference in arterial hypertension have been done with the subjects lying down As it has been shown in healthy subjects that the amount of change in the difference during exercise depends on the position of the body (13) it is not possible directly to compare the results of former studies with those obtained here

None of the six groups of hypertensive subjects in the present study differed significantly from the control subjects in increase in their arteriovenous oxygen difference during exercise This agrees with the results Varnauskas (146) got from patients in the supine position Taylor *et al* (137) on the other hand found that patients disabled by their disease increased their arteriovenous oxygen difference much more during exercise than did normotensive subjects and less disabled hypertensive subjects Other authors examining patients with cardiac decompensation due to arterial hypertension have noted the same (76 100 125)

Arterial hematocrit

At rest The Stage 3 men had a significantly lower mean hematocrit reading in their arterial blood at rest than the control men (table 17) None of the other groups

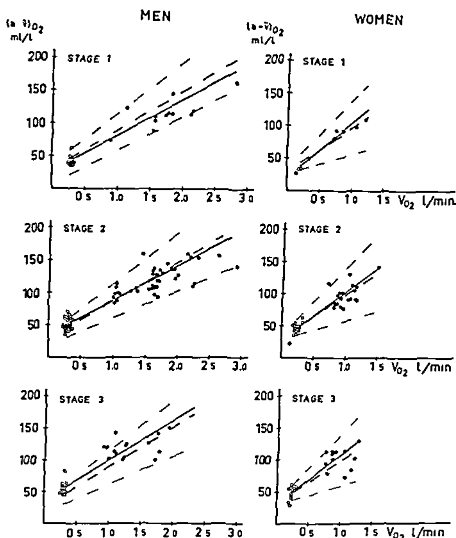

Fig 10 Arteriovenous oxygen difference Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1])	Significance level of difference
Stage 1	Men	$y_x = 26.5 + 56.2\,x$	$y_x = 29.4 + 59.3\,x$	–
	Women	$y_x = 19.1 + 86.5\,x$	$y_x = 29.9 + 67.9\,x$	–
Stage 2	Men	$\bar{y}_x = 34.4 + 55.4\,x$	$y_x = 28.4 + 60.7\,x$	–
	Women	$y_x = 27.3 + 76.7\,x$	$y_x = 31.7 + 67.9\,x$	–
Stage 3	Men	$y_x = 37.7 + 63.5\,x$	$y_x = 28.2 + 61.9\,x$	–
	Women	$y_x = 30.9 + 78.6\,x$	$\bar{y}_x = 32.3 + 67.9\,x$	–

For symbols see Fig 1

---

[1]) *The equations adjusted according to multiple regression functions of the control subjects*
Equations (for V_{O_2} rest, see Fig 1)
Men $\Delta(a-v)O_2/+1.0\,l\,V_{O_2} = 123.4 + 0.408 \times \text{Age} - 41.81 \times \text{BSA}$
Women $(a-v)O_2\,\text{rest} = 32.6 + 0.304 \times \text{Age}$

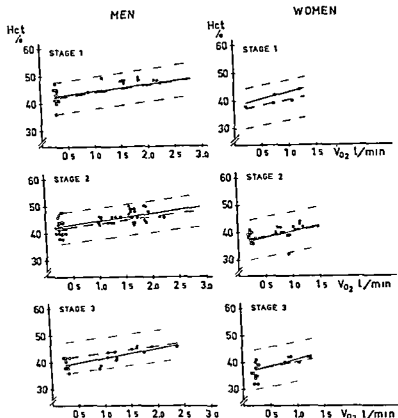

Fig 11 Arterial hematocrit Response to exercise Regression equations

		Hypertensive subjects	Control subjects[1])	Significance level of difference
Stage 1	Men	$y_x = 41\ 8 + 2\ 5\ x$	$y_x = 41\ 4 + 2\ 4\ x$	–
	Women	$y_x = 38\ 3 + 5\ 0\ x$	$y_x = 36\ 5 + 3\ 8\ x$	–
Stage 2	Men	$y_x = 41\ 9 + 2\quad x$	$y_x = 41\ 3 + 2\ 4\ x$	–
	Women	$y_x = 35\ 9 + 4\ 4\ x$	$y_x = 36\ 4 + 3\ 8\ x$	–
Stage 3	Men	$y_x = 38\ 4 + 3\ 4\ x$	$y_x = 41\ 3 + 2\ 4\ x$	<0 01
	Women	$y_x = 30\ 0 + 5\ 1\ x$	$y_x = 36\ 4 + 3\ 8\ x$	<0 0

For symbols see Fig 1

[1]) The equations adjusted according to multiple regression functions of the control subjects Equations for $V_{O_2\ rest}$ see Fig 1

4*

TABLE 17 Arterial hematocrit (per cent) at rest

		Mean ± standard error $\bar{x} \pm s_{\bar{x}}$	Mean diff from the controls $\bar{d}$	Probability p
Stage 1	Men	42.5 ± 0.7	+0.5	–
	Women	39.3 ± 1.4	+2.0	–
Stage 2	Men	42.7 ± 0.5	+0.7	–
	Women	36.9 ± 0.8	–0.4	–
Stage 3	Men	39.4 ± 0.8	–2.6	<0.01
	Women	37.2 ± 1.0	–0.1	–

differed significantly from the control subjects in this respect

Response to exercise On exercise the mean hematocrit level in the arterial blood rose in all six hypertensive groups, as it also did in the control groups (fig 11) In the Stage 3 men it rose significantly more than in the control subjects It also rose more in the Stage 3 women, where the difference was almost significant There were no other significant differences

Comments It seems to be the current opinion that the hematocrit level at rest is not notably different in hypertensive subjects from that in normotensive subjects (54 58, 87, 156) Glazer (58), however, noted a tendency to increased values in the early stages of the disease and a successive fall as the disease progressed but none of his hypertensive groups differed significantly from his normotensive subjects In agreement with this Rowe *et al* (120) found that their subjects with Smithwick grade 1 and 2 hypertension had slightly higher hematocrit readings than subjects with *grade 3 or 4* of the disease, who had the same average value as their control group Tibblin *et al* (141) found that men in their fifties with mild arterial hypertension had a significantly higher hematocrit score than a normotensive control group

The resting values found in the present study indicate that a change in hematocrit is not characteristic of early or established arterial hypertension, but that the hematocrit readings are apt to be low at advanced stages of the disease

The only report in the literature on the effect of exercise on the hematocrit level in hypertension seems to be that of Tibblin *et al* (141) Examining men in their fifties in the supine position they noted that the level rose to about the same extent on exercise as in control subjects This agrees with the observations in the Stage 1 and 2 subjects examined in this study On the other hand, the Stage 3 subjects both men and women, showed a significantly greater rise in hematocrit score on exercise than did the control subjects

study therefore, it was thought best to group them according to the system of classification worked out by the World Health Organization, which is said to be valid for all forms of arterial hypertension. The criteria in question are a synthesis of most systems of classification and take into account both the patients subjective ailments and the objective signs in all the organs primarily affected by hypertension

Like other systems of classification the *WHO* system aims only to class the patients by *the condition they* present It does not take into account that the disease may run different courses in different cases or that different causes may give rise to different sets of signs and symptoms Consequently it was decided to analyze the results from men and women separately as has not been done in most previous studies for one reason because the disease is known to run a more favorable course in women than in men

It was wanted to compare the results from the hypertensive subjects with those from a matched control group but the control subjects could only be matched to a limited extent Thus only a few of the control subjects were hospitalized at the time they were studied the majority being volunteers Nor were the two groups alike in age The results from the hypertensive subjects were corrected for age and anthropometric data however before they were compared with those from the control group and this eliminated to some extent the differences between the two kinds of subjects referable to differences in composition.

Analysis of the results from the hypertensive and control subjects indicated that the patients assigned to different clinical stages differed in hemodynamic pattern and likewise the men and women at the same stage If this signifies that the hemodynamics change gradually as the hypertensive disease develops in different ways in men and women the stages one uses for classifying hypertension must correctly reflect the stage of the disease in both men and women It is not known whether this was so in *the present case* to determine this it is necessary to follow a large series of patients over a long period of time

Oxygen consumption The question is whether the high oxygen uptake at rest of the Stage 1 hypertensive men was due to anxiety or to hypermetabolism or whether a high oxygen uptake is one feature in the hyperkinetic circulation characteristic of this group of patients Even if it is impossible to rule out emotional factors the fact that these patients did not differ from the control subjects in arteriovenous oxygen difference indicates that these factors do not play an important part for the difference is said to be reduced in purely emotionally induced hyperkinetic circulation (77 134) Nor did these patients differ in figures for ventilation or respiratory quotient from the normotensive subjects Nor did they give the impression of being more frightened by the examination than the subjects in the other groups

The thyroid function was not examined in every case but the patients with a consistently elevated heart rate at rest had normal values for basal metabolic

GENERAL DISCUSSION

An account of the hemodynamic alterations in a chronic disease like arterial hypertension must take into consideration a whole series of conditions, such as age and sex, duration of the disease, demonstrable causes, treatment, and kind and severity of organic complications Studies on this subject, therefore, can either be based on a special category of patients, for example, young men with early arterial hypertension, or on a wider population, to show the state of the circulation in the disease in general The aim of the present study was to give a picture of the systemic circulation in hypertensive disease such as it is met with in routine work, i e, in patients of both sexes of working ages with hypertension of varying duration and severity, and probably of different origins

The ideal way to make a clinical study would be to select patients at random from a homogeneous population and compare them with matched control subjects examined under exactly similar conditions and with the same methods As far as known, no previous study using catheterization technics has been done on this pattern and the present study is no exception An investigation is now going on in Bergen Norway with randomly chosen hypertensive patients and normotensive control subjects but so far only preliminary results have been presented (101), these appear to agree with those of the present study

The results reported here were obtained from a series of patients admitted for examination over a period of some years, and examined after 1 to 24 days rest in hospital In view of the spontaneous fall in blood pressure during a hospital stay, often going on for several weeks (86), it would have been good if they could have all been studied after the same number of days in hospital, but this was impossible for practical reasons It would also have been advantageous if none of them had got antihypertensive medication before the studies The medication was stopped three weeks or more previous to the studies in two thirds of the treated cases, and in the cases in which it was stopped later, the results were apparently not affected by the medication The fact that the patients were examined both at rest and during exercise probably outweighs these disadvantages, and no difference was noted in the exercising pattern of response in relation to the length of hospitalization or in relation to whether or not the patient had received any treatment previously

Arterial hypertension is a sign of a chronic disease of complex origin which may take many different courses The subjects examined in the present study represented many different stages of hypertensive disease Different authors have grouped their cases according to different criteria making it hard to compare their results For the present

during exercise in the supine position (49 104) or sitting position (105) This is of practical importance for judging a patient s physical working capacity in terms of heart rate during graded exercise and means that one cannot use the same criteria for a hypertensive subject as one does for a normotensive subject

Arterial blood pressure and pulse pressure Among the Stage 2 and 3 both male and female hypertensive patients the mean blood pressure in the brachial artery increased more on exercise than in the control subjects, others have noted the same in patients with coarctation of the aorta exercising in the supine position (28 136) The hypertensive subjects of the present study also resembled the patients with coarctation in showing a considerable increase in the pulse pressure in the brachial artery during exercise (28 136)

A higher than average rise in arterial blood pressure on exercise has also been observed in other diseases such as coronary heart disease (104 105) and diabetes mellitus (90 91) The Stage 1 men in the present study however did not differ from the control subjects in response of blood pressure to exercise and Gorlin *et al* s (64) patients with an idiopathic elevation in cardiac output at rest also showed a normal response in blood pressure to exercise Patients with essential arterial hypotension have also shown a similar rise in arterial blood pressure and pulse pressure on exercise in the supine position as have normotensive subjects (52)

Cardiac output The male subjects with early arterial hypertension showed a hyperkinetic circulation with a rise in the resting cardiac output As in the case of Holmgren *et al* s (80) patients with vasoregulatory asthenia the rise in cardiac output was not primarily due to an increase in stroke volume in the way it is in the idiopathic high cardiac output state (64) but to an increase in heart rate The latter was also responsible for the abnormal increase in cardiac output observed during rest in Taylor & Donald s (136) patients with coarctation of the aorta Dahlbäck *et al* (28) however reported that the resting cardiac output was normal in 6 out of 8 patients with coarctation of the aorta examined in the supine position

On exercise the Stage 1 hypertensive men showed a smaller rise in the cardiac output in relation to rise in oxygen consumption than did the control group The same was true of the patients with an idiopathic rise in cardiac output described by Gorlin *et al* (64) In other conditions with an abnormally high cardiac output at rest such as "vasoregulatory asthenia (80) coarctation of the aorta (136) anemia (16 133, 147) and hyperthyroidism (16 66), the patients are said to show the same rise in output on exercise in the supine position as control subjects or one that is higher the high cardiac output at rest in these cases thus persisting on exercise

The Stage 3 hypertensive men had a lower cardiac output at rest than the control subjects Whether or not this hypokinetic circulation reflected the beginning of left ventricular failure cannot be judged without measurements of the intraventricular pressure It is unlikely

rate and protein bound iodine Nor were any other clinical signs of hyperthyroidism observed It is hardly likely, *therefore*, that the elevated oxygen consumption at rest in the Stage 1 men was attributable to hyperthyroidism

In all likelihood, therefore, an elevated oxygen uptake at rest is one feature of the disease in these patients with early arterial hypertension A conceivable explanation for this elevation might be an increased production of catecholamines Thus patients with pheochromocytoma generally have a high basal metabolic rate (157), and it has been noted that giving intravenous infusions of epinephrine and norepinephrine to normotensive humans (61) and to dogs (19) causes an increase in oxygen uptake It is generally believed, however, that an increased production of catecholamines is not a prominent feature of most cases of essential or renal arterial hypertension (15, 40, 128) On the other hand, Kuschke (95) reported that, amongst the 20 per cent of his hypertensive patients who occasionally excreted raised amounts of norepinephrine, many had the labile form of the disease

A 15 per cent elevated oxygen consumption at rest in the supine position was also a characteristic feature of Gorlin *et al*'s (64) patients with an idiopathic high cardiac output state All these patients had a normal thyroid function, and it is worthy of note that 5 of their 8 patients showed systolic hypertension at the time they were studied Taylor & Donald (136) observed that an increased cardiac output at rest in the supine position in 20 patients with untreated coarctation of the aorta was associated with a raised oxygen consumption The same has been noted in young patients with aortic stenosis (27) The patients with "vasoregulatory asthenia" described by Holmgren *et al* (80), however, had the same basal oxygen uptake as control subjects

Heart rate Besides an increase in oxygen uptake, the hypertensive men at Stage 1 had an abnormally elevated heart rate at rest, and Taylor & Donald's (136) subjects with coarctation showed the same tendency On the other hand, Gorlin *et al* s (64) patients with an idiopathic elevation in cardiac output had a normal resting heart rate The raised heart rate of the Stage 1 men in comparison with the control subjects, and the lack of a difference in this respect between the Stage 2 and 3 men and the control men indicate a faulty baroceptor function in these subjects corresponding to the reset of the baroceptor mechanisms at higher pressure levels demonstrated by McCubbin *et al* (108) in hypertensive dogs The likelihood of this defect was indicated even more in the female patients, in whom the resting heart rate was elevated at Stage 2 and 3 as well

In essential arterial hypotension, on the other hand the resting heart rate in the supine position is said to be abnormally low (52)

On exercise several of both the male and female hypertensive groups showed a greater rise in heart rate in relation to rise in oxygen consumption than did the control subjects Others have observed the same in coarctation of the aorta during exercise in the supine position (136) and in coronary heart disease

during exercise in the supine position (49, 104) or sitting position (105) This is of practical importance for judging a patient s physical working capacity in terms of heart rate during graded exercise and means that one cannot use the same criteria for a hypertensive subject as one does for a normotensive subject

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that left ventricular failure was responsible, however, for patients with aortic stenosis keep a normal cardiac output *at rest* until their functional capacity is greatly reduced (27, 65, 147) Furthermore, as in most patients with aortic stenosis (27, 147), the cardiac output did not rise less in the Stage 2 and 3 hypertensive men on exercise than it did in the *control subjects* This indicates that the abnormally low resting cardiac output in the Stage 3 men was not caused by *cardiac* insufficiency, for on *exercise* subjects with heart failure often show a lower rise in cardiac output than do normotensive subjects (73, 76, 100, 119, 125) It may be noted that patients with essential arterial hypotension have a low cardiac output at rest, but on exercise *in the* supine position the output rises the same as it does in normotensive subjects (52)

Stroke volume In the idiopathic high cardiac output state the stroke volume at rest is reported to be twice the normal volume (64) This was not true of the men with early arterial hypertension in the present study, nor is it true of other conditions with an abnormally high cardiac output at rest, such as coarctation of the aorta, 'vasoregulatory asthenia' hyperthyroidism and anemia where the resting stroke volume generally does not deviate from that in control subjects (1, 16, 66, 80, 85, 136)

As mentioned neither the cardiac output nor the clinical signs in the present subjects indicated that left ventricular failure was of noteworthy significance in any of the groups One must look elsewhere for the explanation for the lower stroke volume at rest in the Stage 3 men and the Stage 2 and 3 women It may be that it can be traced to the vascular resistance in the systemic circulation, as it has been shown experimentally (55, 70, 149) and clinically (75 156) that the stroke volume at rest is inversely proportional to *the vascular* resistance in the systemic circulation Thus, the mean values for the systemic vascular resistance which were about the same for the Stage 3 men and the Stage 2 and 3 women were the highest among all the hypertensive groups and the stroke volume was reduced to the same extent in all three groups

The observation that the stroke volume did not increase on exercise in the patients with early arterial hypertension as it did in the control subjects tallies with the observations during exercise in the supine position in patients with an idiopathic elevation in cardiac output (64) and untreated coarctation of the aorta (136) On the other hand it has been observed that patients with vasoregulatory asthenia do not differ from control subjects in stroke volume during exercise in the supine position (80) nor did the 8 patients with coarctation of the aorta described by Dahlback *et al* (28), but 6 of them had apparently the same cardiac output at rest as control subjects

The Stage 2 and 3 men and Stage 3 women in the present study also showed a lower rise in stroke volume on exercise than the control subjects the men showing an almost significant difference in this respect A lower than normal rise, or drop in stroke volume has been said to be a manifestation of impaired cardiac function (100, 119), but in view

of what has just been said and of the fact that these groups of hypertensive subjects had still higher values than the control subjects for systemic vascular resistance on exercise cardiac insufficiency can hardly have been a major reason for the abnormally low rise in stroke volume in the hypertensive subjects in the present study

Systemic vascular resistance and conductance A reduction in systemic vascular resistance is said to be a prime factor in most hyperkinetic states including the idiopathic high cardiac output state (64) The Stage 1 men in the present study however showed the same values for systemic resistance at rest as the control subjects That a hyperkinetic circulation does not exclude the possibility of an increase in systemic resistance is proved by the observations of Taylor & Donald (136) in patients with untreated coarctation of the aorta

An elevated systemic resistance at rest is not only seen in patients with established or advanced stages of hypertension It has been noted in coronary heart disease (104 105) cardiac insufficiency (42) diabetes mellitus (91) and mitral valvular disease (37 43 67) Among the patients with mitral disease the ones with atrial fibrillation have higher values for systemic resistance than ones with a sinus rhythm The high systemic resistance in some of these conditions is thought to be due to the development of compensatory peripheral vasoconstriction to keep the blood pressure normal when the cardiac output is lowered (42)

On exercise, all the hypertensive subjects in the present study showed some reduction in systemic resistance but all showed highly significantly lower mean rises in systemic conductance than the control subjects This points to reduction of the peripheral vascular bed present already in the early stages of the disease Whether a reduction of this kind might be due to inadequate vasodilation because of organic changes in the vascular walls or to an abnormal distribution of blood is a question to which the present study gives no answer Plethysmographic studies of hypertensive patients after maximum vasodilation however point to structural changes in the peripheral vascular bed in patients with arterial hypertension (25 47) A recent morphologic study (127) indicates that the structural alterations are not due to hypertrophy or hyperplasia of the vascular walls but to a persistent shortening of the circular elements in the walls of the arterioles Animal experiments have shown that arterial hypertension is accompanied by an increase in the elastic stiffness of the walls of the arteries probably because of changes in the composition of the vascular walls (41)

An abnormally high systemic resistance during exercise has also been observed in untreated coarctation of the aorta (136) and in conditions such as coronary disease (104) and diabetes mellitus (91) But patients with mitral valvular disease having an elevated systemic resistance at rest are said to show normal values during exercise in the supine position (67) In Frick s study of essential arterial hypotension the systemic resistance did not differ from that of a control group

either at rest or during exercise in the supine position (52)

Arteriovenous oxygen difference Most conditions characterized by an elevated cardiac output at rest, such as anemia (16, 147), hyperthyroidism (16, 66, 144, 147), the idiopathic high cardiac output state (64), 'vasoregulatory asthenia" (80) and anxiety (77, 134), are said to be usually associated with an abnormally low arteriovenous oxygen difference This was not true of the Stage 1 hypertensive men in the present investigation and this, together with their raised oxygen uptake at rest, indicates that the elevated cardiac output was of metabolic origin in their case The same results have been obtained on examination of patients with untreated coarctation of the aorta showing an elevated cardiac output at rest (136) These patients, like the Stage 1 men did not differ significantly from the control subjects in arteriovenous oxygen difference during exercise

A wide arteriovenous oxygen difference at rest is said to be a sign of cardiac insufficiency (43, 110) That this was not so in the case of the Stage 2 and 3 men here is indicated by the fact that on exercise the difference widened to the same extent in these men as in the control subjects, and they also showed the same rise as the control subjects in cardiac output, in cardiac insufficiency the arteriovenous oxygen difference increases more, and the cardiac output less, than it does in "compensated patients (76, 100, 110, 125) It is more likely therefore, that the wide arteriovenous oxygen difference in the Stage 2 and 3 men at rest was caused by changes in the peripheral blood flow and the distribution of blood to different areas and probably also inside the separate organs as well

Hematocrit level It has been suggested from observations in animal experiments (98, 99) that the cardiac output is raised in early arterial hypertension because of an increase in circulating blood volume and a number of observations in humans support this hypothesis (35, 58, 59, 145) The normal hematocrit score at rest in the Stage 1 subjects here does not bear this out, but nor does it exclude the possibility that an increase in circulating blood volume might be the primary reason for the raised cardiac output at rest in subjects with early arterial hypertension Studies in which the volume of blood (45) or plasma (11) was measured have not pointed to an increase in the volume of blood in early arterial hypertension even when the cardiac output at rest is raised

The lower hematocrit score at rest in the Stage 3 men than in the control subjects might indicate that the volume of circulating blood had increased because of cardiac insufficiency (43 156) This seems unlikely however in view of what has just been said about cardiac insufficiency in this group Though only one patient showed a slightly reduced hemoglobin content, it is not impossible that anemia might have been responsible for the low hematocrit level in this group

Thus the present study does not permit any conclusions on the total volume of blood in arterial hypertension For this direct measurements are needed

SUMMARY

A study was made in human subjects of how a raised arterial blood pressure affects the systemic circulation at rest and during exercise

Ninety nine subjects with arterial hypertension of different degrees and origins were used—64 men and 35 women Their ages ranged between 17 and 64 They were classified according to the recommendations of the World Health Organization into Stage 1 characterized by early arterial hypertension without signs of organic changes in the cardiovascular system Stage 2 or established hypertension with signs of cardiovascular hypertrophy but no other evidence of organic damage and Stage 3 or advanced hypertension with evidence of organic damage attributable to the hypertensive disease

The results from these subjects were compared with those from 87 subjects with no signs or symptoms of cardiovascular disease—59 men and 28 women between the ages of 16 and 59 Sixty one of the control subjects were healthy volunteers the rest were hospital patients with no signs of cardiovascular disease or other disease relevant to the investigation

The subjects were examined in the morning in the fasting state First the resting values with the patient sitting were determined for heart rate intra arterial blood pressure cardiac output (determined with the dye dilution technic and bromsulphalein as indicator) and oxygen consumption Then the effect of exercise on these values was studied with the subjects sitting on an electrically braked bicycle ergometer Thirty two hypertensive subjects exercised for two periods of 10 to 12 minutes each first at a low level and then at a level just under what it was assumed they could stand Thirty six hypertensive subjects exercised for only one period at a level just under what it was assumed they could stand The remaining hypertensive subjects exercised for only one period at a low level, not going on to another period for various reasons

To determine the reproducibility of the values obtained repeat resting measurements were made after a short interval in 20 hypertensive subjects and measurements were made during two consecutive periods of exercise at the same level in 11 hypertensive subjects

The data from both the hypertensive and control subjects were fed into a computer for analysis The response to exercise was related to increase in oxygen consumption, and the changes in the values for different functions on exercise were expressed in the form of regression equations Before the values for the hypertensive series were compared with those from the control series they were corrected for age and anthropometric variables on the basis of multiple regression analysis of the control data

The consecutive determinations at rest and during exercise revealed a systematic

error between 0 1 and 7 1 per cent for the functions measured, and an error for the single determination ranging between 1 2 and 9 6 per cent The systolic blood pressure was significantly lower at the second measurement both during rest and exercise, and likewise the mean blood pressure during exercise The other variables showed no significant differences between consecutive measurements

Oxygen consumption The Stage 1 men had a significantly higher oxygen uptake at rest than the control men No other observations of note were made about oxygen consumption

Heart rate The Stage 1 men and Stage 2 and 3 women had significantly higher heart rates at rest than the control subjects On exercise the Stage 2 and 3 men and the Stage 1 and 3 women raised their rate significantly more than did the control subjects

Brachial artery blood pressure At rest, all the hypertensive groups had significantly higher brachial artery blood pressures than the control subjects On exercise, the Stage 2 and 3 men and women raised their mean arterial pressures significantly more than did the control subjects The same was true of the Stage 2 and 3 men and the Stage 3 women for systolic blood pressure The Stage 1 men and women on the other hand did not show a significantly different increase in systolic or mean arterial pressure on exercise in comparison with the control subjects In the Stage 3 women, the diastolic pressure also rose significantly more on exercise than in the control subjects but not in the other hypertensive groups

Pulse pressure At rest, all the hypertensive groups had a significantly higher pulse pressure than the control subjects On exercise, the pulse pressure rose significantly more in the Stage 2 men and Stage 3 women than in the control subjects, but not in the other hypertensive groups

Cardiac output At rest the Stage 1 men had a significantly high cardiac output, and the Stage 3 men a significantly low output, but the other men and the women did not differ significantly from the control subjects in these values On exercise, the output rose significantly less in the Stage 1 subjects of both sexes than in the control subjects but not in any of the other hypertensive groups

Stroke volume The stroke volume was significantly low at rest in the Stage 3 men and women, and also in the Stage 2 women The other hypertensive groups did not differ significantly from the control subjects in their resting stroke volume On exercise, the volume tended to rise less than in the control subjects, or fall in all the hypertensive groups except the Stage 2 women the differences from the controls being significant for the three male hypertensive groups and Stage 1 women

Systemic vascular resistance and conductance At rest all the hypertensive groups except the Stage 1 men showed a significantly high systemic vascular resistance and a significantly low systemic vascular conductance in comparison with the control subjects On exercise, the vascular resistance fell in all six hypertensive groups The Stage 2 and 3 sub

jects both men and women raised their mean arterial pressure significantly high in relation to the rise in cardiac output, but the Stage 1 hypertensive subjects did *not differ* significantly from the control subjects in this respect On exercise, the systemic vascular conductance rose significantly less in all the hypertensive groups of both sexes than in the corresponding control groups

Arteriovenous oxygen difference The resting arteriovenous oxygen difference was significantly wide in the hypertensive men at Stage 2 and 3 but the Stage 1 men and the female hypertensive groups did not differ significantly from the control subjects in their resting difference None of the hypertensive groups differed significantly from the control subjects in the amount the difference widened on exercise

Arterial hematocrit At rest the Stage 3 men had a significantly low hematocrit reading in their arterial blood but the other hypertensive groups did not differ significantly from the control subjects in this respect On exercise the hematocrit level in the arterial blood rose significantly more in the Stage 3 men and women than in the control subjects but not in the other hypertensive groups

Thus it would appear from the present investigation that the hemodynamic pattern at rest and during exercise of men and women with arterial hypertension of different stages differs in many respects from that in control subjects

The values obtained from the hypertensive men indicate that early arterial hypertension is characterized by a hyperkinetic circulation at rest and a normal systemic vascular resistance that established hypertension is characterized by an eukinetic resting circulation and a raised systemic vascular resistance and that advanced hypertension is characterized by a hypokinetic circulation and a raised systemic vascular resistance at rest But the fact that the systemic vascular conductance rose significantly less on exercise in all three male hypertensive groups than in the control subjects including Stage 1 indicates that the peripheral vascular bed is reduced even in the earliest stages of arterial hypertension.

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APPENDIX

TABLE I Age anthropometric and clinical data

Pat	Age	Height cm	Weight kg	BSA m^2	Clinical diagnosis	Known duration of art hyp years	Highest casual BP recorded mm Hg	Previous antihyp treatment	Heart volume ml/m^2 BSA	Hospital stay before study days
Hypertensive men Stage 1										
1 O G	17	174	61 5	1 4	*EH*	<1/2	180/110	—	290	1
2 B.H	17	171	51 9	1 60	*EH*	1	215/90	—	260	2
3 J G	18	180	66 6	1 84	*CG*	<1/2	155/95	—	490	14
4 B K	18	170	76 2	1 88	*EH*	1/2	180/100	—	300	1
5 K.K.	23	179	63 4	1 80	*EH*	<1/2	220/95	—	400	4
6 S.J	30	187	83 0	2 08	*EH*	<1/2	165/100	—	340	3
7 R.M	32	182	67 5	1 87	*EH*	1/2	215/135	+	350	10
8 S.A	37	186	72 8	1 96	*EH*	<1/2	170/95	—	380	2
9 M.I	39	169	71 2	1 9	*EH*	<1/2	190/110	+	300	4
10 B S	43	178	74	1 92	*EH*	1	200/115	+	360	3
11 B P	47	172	76 6	1 90	*EH*	<1/2	230/120	—	460	2
12 C O	53	171	71 6	1 83	*EH*	4	180/100	—	370	9
13 H G	57	170	90 1	2 02	*EH*	<1/2	180/105	—	430	4
14 P W	58	168	73 4	1 82	*EH*	4	200/100	—	380	3
Hypertensive men Stage 2										
15 G H	25	178	77 8	1 95	*EH*	<1/2	205/140	—	440	1
16 L S	25	173	87 4	2 01	*EH*	<1/2	190/105	—	380	1
17 G J	38	173	70 5	1 83	*CG*	6	200/120	+	330	—
18 S L.	38	1 3	80 5	1 94	*EH*	<1/2	250/120	+	400	6
19 A K	40	175	84 3	2 00	*EH*	3	180/95	—	350	4
20 E O	43	177	115 0	2 30	*EH*	<1/2	230/130	—	—	15
21 P E	44	182	107 1	2 28	*EH*	<1/2	170/105	—	450	1
22 B E	44	166	68 2	1 6	*EH*	<1/2	240/160	+	380	4
23 S H	45	171	75 1	1 87	*RVH*	<1/2	165/115	—	410	2
24 T.J	45	168	78 0	1 87	*EH*	<1/2	220/120	—	390	3
25 A P	45	172	71 8	1 84	*EH*	12	230/130	+	—	7
26 T P	45	183	90 1	2 12	*EH*	<1/2	180/130	—	470	3
27 E E	46	1 8	74 4	1 92	*EH*	1	175/125	—	410	3
28 F B	47	1 5	75 3	1 90	*EH*	10	190/120	—	480	2
29 A H	47	171	76 0	1 88	*EH*	7	170/115	—	440	8
30 N J	48	182	66 8	1 86	*PK*	<1/2	200/135	—	480	7
31 I N	48	172	79 9	1 93	*EH*	<1/2	220/120	—	480	3
32 T O	48	176	65 8	1 80	*EH*	<1/2	250/130	—	460	5
33 A K	49	169	93 9	2 08	*EH*	4	250/150	—	390	6
34 S O	49	191	81 9	2 09	*CG*	-	240/110	—	420	13
35 1 F	50	180	92 9	2 1[illegible]	*EH*	<1/2	230/115	—	460	2
36 S.S	50	1 8	107 0	2 [illegible]4	*EH*	<1/2	210/135	—	570	1
3 L.U	50	182	98 3	2 19	*EH*	7	200/150	+	410	6
38 H L.	51	1 6	72 8	1 88	*EH*	3	260/—	+	480	4
39 S.M	51	175	92 0	2 0	*EH*	12	230/130	+	400	2

Table I (continued)

Pat		Age	Height cm	Weight kg	BSA m^2	Clinical diagnosis	Known duration of art hyp years	Highest casual BP recorded mm Hg	Previous antihyp treatment	Heart volume ml/m^2 BSA	Hospital stay before study days
40	R A	52	169	61 1	1 70	*CP*	3	280/–	+	340	1
41	G H	52	172	76 5	1 89	*EH*	12	250/160	–	400	4
42	A K	52	183	118 1	2 38	*EH*	10	210/135	–	410	3
43	K K.	52	174	88 5	2 03	*EH*	10	210/135	–	470	20
44	S K	52	166	66 7	1 74	*RVH*	7	300/150	+	410	2
45	S L	52	175	67 2	1 81	*EH*	5	240/110	–	410	5
46	N S	52	171	66 6	1 78	*EH*	<1/2	175/120	–	360	4
47	V O	53	176	82 7	1 99	*FH*	<1/2	180/105	–	450	2
48	P L	56	167	81 2	1 90	*FH*	10	200/120	+	370	12
49	H S	57	171	76 8	1 89	*EH*	<1/2	285/140	+	410	1
50	N H	58	175	80 7	1 86	*EH*	2	170/110	+	350	3
51	I N	58	183	70 0	1 90	*RVH*	6	245/120	–	500	4
						Hypertensive men Stage 3					
52	K S	34	172	65 5	1 77	*EH*	<1/2	240/150	+	320	7
53	E J	36	175	70 8	1 85	*EH*	<1/2	180/130	–	310	11
54	A J	36	175	60 4	1 72	*CG*	13	230/160	+	420	2
55	L O	44	183	94 3	2 16	*EH*	1	250/150	+	430	20
56	G C	48	172	72 5	1 85	*EH*	5	190/130	–	520	3
57	F B	49	183	77 5	1 99	*EH*	6	220/140	+	–	7
58	A G	50	180	80 1	2 00	*CG*	3	210/130	+	520	2
59	M H	51	183	93 8	2 16	*EH*	<1/2	250/150	+	–	11
60	A L	52	176	81 0	1 97	*EH*	2	190/120	–	310	3
61	S K	54	167	78 1	1 87	*EH*	5	250/170	–	450	12
62	R G	59	173	66 7	1 79	*EH*	<1/2	215/125	–	660	2
63	H A	60	185	91 4	2 15	*EH*	6	250/170	+	790	8
64	O E	64	178	86 4	2 04	*EH*	2	260/150	+	470	8
						Hypertensive women Stage 1					
65	V S	23	159	58 5	1 60	*EH*	<1/2	180/115	–	330	1
66	U T	31	173	71 1	1 84	*PH*	7	240/135	–	370	4
67	M P	49	157	54 9	1 54	*EH*	8	205/125	–	320	2
68	G R	53	162	53 0	1 55	*EH*	<1/2	195/110	–	340	14
						Hypertensive women Stage 2					
69	M E	32	161	63 8	1 69	*EH*	6	200/140	–	310	8
70	U B	35	163	60 2	1 64	*PH*	5	250/140	+	310	7
71	V E	36	158	55 0	1 55	*PH*	3	220/130	–	340	3
72	O A	39	160	78 8	1 82	*EH*	<1/2	215/120	–	380	5
73	M B	41	166	71 2	1 79	*EH*	13	200/120	+	350	14
74	I S	43	165	53 3	1 64	*RVH*	11	230/130	+	360	4

Table I (continued)

Pat	Age	Height cm	Weight kg	BSA m²	Clinical diagnosis	Known duration of art.hyp years	Highest casual BP recorded mm Hg	Previous antihyp treatment	Heart volume ml/m² BSA	Hospital stay before study days
75 M L	44	158	60 6	1 61	*EH*	4	240/130	+	340	4
76 K A	45	151	69 1	1 65	*EH*	<1/2	260/155	+	320	4
77 M J	45	162	57 1	1 60	*EH*	25	210/130	−	360	7
78 I O	47	167	61 1	1 68	*CP*	1	210/125	−	290	4
79 E H	52	152	41 0	1 33	*CP*	14	230/130	+	350	24
80 K J	52	165	70 6	1 78	*EH*	2	2[illegible]0/120	−	310	4
81 E F	54	156	82 9	1 8[illegible]	*CP*	1	230/130	−	460	13
82 A S	54	156	99 3	1 97	*EH*	27	280/170	+	380	7
83 K T	59	160	66 0	1 69	*CP*	<1/2	230/115	−	330	3
84 L Ö	60	163	70 6	1 76	*CP*	23	300/150	+	450	24
85 D S	61	171	66 9	1 78	*RVH*	7	250/130	−	410	4
					Hypertensive women, Stage 3					
86 A O	38	168	62 4	1 [illegible]0	*PH*	1	210/115	+	310	11
87 M O	41	165	76 5	1 84	*EH*	<1/2	180/130	−	330	9
88 G K	42	165	70 4	1 [illegible]7	*EH*	<1/2	170/115	−	440	3
89 K B	44	170	68 8	1 79	*EH*	10	250/150	+	650	20
90 D Ö	47	172	64 6	1 [illegible]6	*EH*	13	230/110	+	450	6
91 G B	49	152	54 9	1 50	*EH*	<1/2	230/130	−	550	6
92 A J	49	169	75 1	1 86	*EH*	1	190/105	−	360	16
93 M S	49	165	78 4	1 86	*EH*	<1/2	250/160	−	320	8
94 E J	51	168	56 8	1 64	*EH*	1	2[illegible]0/120	−	410	6
95 G B	56	155	68 3	1 67	*CP*	13	200/110	+	440	9
96 E K	57	161	65 0	1 64	*RVH*	10	210/120	+	490	2
97 [illegible] A	58	162	70 0	1 [illegible]5	*EH*	2	190/115	−	5[illegible]0	2
98 L G	59	152	80 6	1 [illegible]7	*EH*	1	270/130	−	450	1
99 S S	62	165	71 3	1 [illegible]8	*EH*	20	280/140	−	530	6

CG=chronic glomerulonephritis *CP*=chronic pyelonephritis *EH*=essential hypertension *PH*=post toxemic hypertension *PK*=polycystic kidneys, and *RVH*=renovascular hypertension.

TABLE II Individual hemodynamic data

Pat	State	$\dot{V}_{O_2}$	HR	$P_{S_{BA}}$	$P_{D_{BA}}$	$\bar{P}_{BA}$	Q	SI	SVR	$(a-v)_{O_2}$	Hct
					Hypertensive men, Stage 1						
1	R'	0 28	89	149	81	102	7 6	85	13 4	37	43
	R''	0 27	90	140	74	96	6 7	74	14 3	40	42
	E_I	1 57	163	185	68	111	14 9	91	7 5	105	47
	E_{II}	2 25	190	200	85	123	17 0	90	7 2	133	47
2	R	0 31	100	147	80	105	8 9	89	11 8	34	45
	E	2 81	200	220	92	140	17 2	86	8 1	164	51
3	R	0 27	73	121	74	91	4 0	55	22 8	68	41
	E_I	1 77	155	182	86	119	15 3	99	7 8	116	43
	E_{II}	2 65	184	198	88	122	19 3	105	6 3	137	45
4	R	0 28	86	144	79	105	8 3	97	12 7	34	45
	R''	0 29	82	138	79	103	7 1	87	14 5	40	44
	E_I	1 57	170	164	89	119	14 1	83	8 4	111	48
	E_{II}	1 84	173	160	80	111	16 0	92	6 9	115	48
5	R'	0 30	84	154	88	108	8 0	95	13 5	38	44
	R''	0 30	75	153	84	110	7 6	101	14 5	40	44
	E	1 54	168	213	88	118	17 2	102	6 9	89	48
6	R	0 29	69	128	76	94	6 1	88	15 4	48	36
	E	1 68	127	160	79	107	12 2	96	8 8	137	37
7	R	0 34	66	166	102	127	9 0	136	14 1	38	41
	E_I	0 90	118	203	116	150	12 2	103	12 3	74	44
	E_{II}	1 47	169	212	113	145	14 6	86	9 9	101	44
8	R	0 31	66	128	72	90	7 0	106	12 9	43	43
	E	1 54	120	174	86	116	13 2	110	8 8	117	46
9	R	0 28	118	169	100	122	8 0	68	15 3	36	45
	E	2 19	208	211	96	131	14 2	68	9 2	154	48
10	R	0 27	81	151	84	108	7 1	88	15 2	39	41
	E	2 16	182	209	102	150	18 3	100	8 3	120	45
11	R	0 33	94	152	84	111	8 6	92	12 9	38	42
	E	1 74	184	240	110	153	15 4	84	9 9	113	47
12	R	0 30	92	160	86	110	6 5	71	16 9	46	40
	E	1 41	169	204	84	123	10 5	62	11 7	134	42
13	R	0 30	70	138	85	109	4 9	70	22 3	61	42
	E	2 12	153	253	122	177	18 6	122	9 5	114	48
14	R	0 28	67	153	80	102	6 6	98	15 5	42	47
	E_I	1 15	106	174	97	129	9 3	88	13 9	124	49
	E_{II}	1 53	152	210	103	142	12 5	82	11 4	146	49

Table II (continued)

Pat	State	V_{O_2}	HR	$P_{S_{BA}}$	$P_{D_{BA}}$	$\overline{P}_{BA}$	Q	SV	SVR	$(a-\bar{v})_{O_2}$	Hct
					Hypertensive men Stage 2						
15	R	0.35	73	192	119	151	7.2	99	21.0	48	42
	E	1.[illegible]4	180	280	129	179	13.3	74	13.5	131	46
16	R	0.30	96	135	84	101	5.9	61	17.1	51	40
	E	1.88	190	185	91	120	13.6	72	8.8	138	45
17	R	0.26	83	156	103	119	5.3	64	22.4	49	42
	R	0.25	82	157	101	121	5.2	63	23.3	48	42
	E	1.66	185	222	95	134	13.9	75	9.6	119	44
	E	1.73	185	220	96	132	15.1	82	8.7	114	44
18	R	0.31	79	152	88	110	7.2	91	15.3	44	42
	E_I	0.99	106	199	93	125	10.7	101	11.7	93	44
	E_{II}	1.59	129	224	97	137	12.3	95	11.1	129	44
19	R	0.27	83	139	79	100	7.4	89	13.5	35	47
	E_I	1.62	139	185	85	115	16.5	119	7.0	98	49
	E_{II}	2.89	174	200	85	122	20.3	117	6.0	142	51
20	R	0.33	83	172	111	137	6.3	76	21.7	52	40
	R	0.32	81	159	102	125	6.5	80	19.2	49	40
	E	1.98	165	221	114	149	15.6	95	9.6	127	43
	E	2.07	170	207	108	145	15.6	93	9.3	133	43
21	R	0.32	75	163	103	125	5.6	75	22.3	58	38
	E_I	1.81	132	192	103	132	12.5	95	10.6	145	42
	E_{II}	2.61	164	225	105	140	16.4	100	8.5	159	44
22	R	0.23	65	210	126	155	5.0	77	31.8	46	42
	E	1.67	150	280	136	198	14.0	93	14.1	119	49
23	R	0.29	58	156	87	112	5.1	88	22.0	57	44
	E_I	1.03	105	191	104	137	9.5	91	14.4	109	46
	E_{II}	1.69	140	214	111	152	11.5	82	13.2	147	48
24	R	0.33	55	152	88	116	5.3	96	21.9	62	44
	E	2.29	1[illegible]0	261	132	179	14.9	88	12.0	154	50
25	R	0.29	94	207	116	159	7.4	79	21.5	40	44
	E	1.58	181	274	141	210	14.8	82	14.2	107	50
26	R	0.27	55	163	98	122	6.0	109	20.3	45	44
	E_I	1.06	74	203	117	153	10.6	143	14.4	100	46
	E_{II}	1.33	88	204	112	150	12.4	141	12.1	107	46
27	R	0.26	57	181	112	137	5.2	91	26.4	50	41
	E_I	1.19	112	216	122	160	11.1	99	14.4	107	44
	E_{II}	1.53	160	233	127	165	14.5	91	11.4	106	45
28	R	0.29	79	196	120	133	4.0	51	34.5	71	44
	E	1.44	149	237	120	168	9.0	60	18.7	160	48

Table II (continued)

Pat	State	V_{O_2}	HR	$P_{S_{BA}}$	$P_{D_{BA}}$	$\bar{P}_{BA}$	Q	SV	SVR	$(a-\bar{v})_{O_2}$	Hct
29	R	0.27	54	169	97	122	4.5	83	27.1	61	40
	E	1.03	121	190	112	144	9.0	74	16.0	114	43
30	R	0.25	55	167	91	118	5.5	100	21.4	46	42
	R''	0.26	54	162	91	119	5.3	98	22.4	48	43
	E	1.01	114	209	107	146	10.3	90	14.2	98	44
31	R	0.27	65	151	87	110	5.4	83	20.4	50	44
	R''	0.26	67	146	84	110	5.1	76	21.0	52	44
	E	1.63	148	248	102	154	14.5	100	10.4	110	46
32	R	0.24	64	181	102	128	4.8	75	26.7	49	43
	E	1.58	149	287	124	182	11.8	79	15.4	134	47
33	R	0.37	81	222	130	170	8.6	106	19.8	43	42
	E	2.24	156	283	147	205	19.0	126	10.5	115	46
34	R	0.26	58	169	93	120	5.7	98	21.0	46	40
	E'	1.65	140	310	110	172	20.1	138	8.6	82	46
	E''	1.67	154	298	112	162	17.8	114	9.2	95	43
35	R	0.38	56	192	96	126	6.7	120	18.8	57	40
	E	2.49	162	262	130	189	19.9	123	9.5	125	46
36	R	0.32	73	163	105	127	7.8	107	16.3	41	48
	E'	1.86	126	230	117	167	15.2	121	11.0	122	50
	E''	1.96	130	212	112	155	16.8	129	9.2	117	50
37	R	0.34	64	161	98	126	5.7	89	22.1	60	42
	E_I	1.26	121	210	115	149	11.3	93	13.2	112	44
	E_{II}	1.91	152	225	116	156	13.9	91	11.2	137	44
38	R	0.26	68	176	89	121	5.4	79	22.4	47	43
	E	1.94	169	252	124	185	15.9	94	11.6	122	45
39	R	0.31	65	172	99	128	5.0	86	22.8	54	48
	E	1.87	145	262	125	185	14.6	101	12.7	128	50
40	R	0.27	102	201	105	145	5.7	56	25.4	48	42
	R'	0.23	103	188	102	131	5.3	52	24.5	42	43
	E	1.05	155	251	111	170	11.9	77	14.3	88	44
41	R	0.32	82	237	134	176	6.6	81	26.7	48	46
	E_I	1.02	111	278	148	196	12.2	110	16.1	84	50
	E_{II}	1.61	120	270	137	188	14.9	124	12.6	108	49
42	R'	0.34	76	155	93	120	7.2	95	16.7	48	52
	R''	0.34	74	150	90	112	7.2	97	15.6	47	52
	E	1.64	122	204	102	142	12.7	104	11.2	129	55
43	R	0.26	65	180	97	125	6.8	105	18.4	39	38
	E	1.36	143	225	111	152	13.2	92	11.5	103	40
	E'	1.39	146	186	101	130	14.4	93	9.0	97	38

Table II. (continued)

Pat	State	$\dot V O_2$	HR	$P_{S_{BA}}$	$P_{D_{BA}}$	$\bar P_{BA}$	Q	SV	SVR	$(a-\bar v)O_2$	Hct
44	R	0.20	54	198	99	135	3.7	69	36.5	55	40
	E	2.13	161	303	130	203	13.3	83	15.3	160	44
45	R'	0.33	64	181	85	120	6.8	106	17.7	49	43
	R''	0.31	59	182	83	119	6.5	110	18.3	48	43
	E_I	1.07	104	212	92	138	10.8	104	12.8	99	45
	E_{II}	1.63	165	247	110	162	14.8	90	10.9	110	46
46	R	0.24	76	178	111	136	3.9	51	34.9	61	46
	E	1.61	146	212	105	149	11.7	80	12.7	138	48
	E	1.59	150	210	110	150	10.0	67	15.0	159	49
47	R	0.59	48	152	73	100	5.5	115	18.2	52	40
	E	1.69	126	199	78	116	12.5	99	9.3	135	44
48	R	0.3[illegible]	65	199	115	147	5.3	82	27.8	60	44
	E	1.26	100	201	111	155	10.1	101	15.4	125	46
49	R	0.30	66	215	105	148	6.9	105	21.4	44	40
	E	1.2	158	232	119	159	12.2	77	13.0	104	44
	E	1.[illegible]1	154	226	104	145	12.4	81	11.7	97	44
50	R	0.26	62	141	90	113	4.[illegible]	68	26.9	61	42
	E	2.17	170	210	112	152	13.9	82	10.9	155	46
51	R	0.[illegible]8	64	223	109	156	6.3	98	24.8	44	40
	E	1.6[illegible]	158	290	144	208	14.8	94	14.1	109	42

Hypertensive men Stage 3

Pat	State	$\dot V O_2$	HR	$P_{S_{BA}}$	$P_{D_{BA}}$	$\bar P_{BA}$	Q	SV	SVR	$(a-\bar v)O_2$	Hct
52	R	0.[illegible]8	84	177	112	139	5.3	63	26.2	52	41
	R	0.32	83	173	109	135	8.0	96	16.9	59	41
	E_I	0.99	127	222	107	150	9.7	76	15.5	102	43
	E_{II}	1.55	179	268	126	168	14.4	80	11.7	108	45
53	R	0.30	83	162	114	130	6.1	73	21.3	49	39
	E	1.89	182	204	122	160	16.3	90	9.8	116	43
54	R	0.79	85	232	163	188	6.3	74	29.8	45	38
	E_I	1.24	130	256	168	204	10.3	76	19.7	171	41
	E_{II}	1.59	167	274	170	209	12.6	76	16.6	127	42
55	R	0.31	66	210	119	146	5.7	86	25.6	55	39
	E_I	1.[illegible]1	119	248	129	172	12.1	102	14.2	100	44
	E_{II}	1.77	157	273	129	177	15.7	100	11.3	113	44
56	R	0.29	73	185	108	135	6.4	88	21.1	45	33
	E	1.[illegible]1	144	232	115	165	17.1	119	9.7	100	38
[illegible]	R	0.33	62	208	115	149	5.1	82	29.2	64	36
	E	0.91	122	247	135	173	7.6	62	22.8	120	38

Table II (continued)

Pat	State	V_{O_2}	HR	$P_{S_{BA}}$	$P_{D_{BA}}$	$\overline{P}_{BA}$	Q	SV	SVR	$(a-v)_{O_2}$	Hct
58	R	0 24	74	202	114	142	5 2	70	27 3	47	42
	E_I	1 07	118	259	125	173	9 5	81	18 2	113	45
	E_{II}	1 64	167	286	133	182	14 2	85	12 8	116	46
59	R	0 28	63	187	105	135	4 5	71	30 0	62	40
	E	2 39	172	312	125	185	17 2	100	10 8	139	46
60	R	0 30	68	178	92	125	6 1	90	20 5	49	44
	E	1 22	138	218	108	153	11 7	85	13 1	104	46
61	R	0 27	63	191	108	141	4 9	78	28 8	54	42
	E_I	1 09	117	239	122	163	9 9	85	16 5	110	44
	E_{II}	1 92	158	235	127	167	12 7	80	13 2	151	46
62	R	0 28	62	186	101	129	4 7	76	27 5	59	38
	E	1 25	113	243	111	158	10 1	89	15 7	124	42
63	R	0 31	55	191	104	134	3 8	69	35 3	82	38
	E	1 08	136	207	112	146	7 6	56	19 2	142	42
64	R	*0 36*	69	221	119	152	5 1	74	29 8	*70*	42
	E_I	*1 42*	133	274	139	185	10 5	79	17 6	*135*	45
	E_{II}	*1 75*	152	295	119	165	12 3	81	13 4	*142*	46
						Hypertensive women, Stage 1					
65	R	0 29	51	162	85	113	5 3	104	21 3	54	41
	E	1 21	178	214	120	155	11 1	62	14 0	109	44
66	R	0 15	79	197	118	147	5 7	72	25 8	27	42
	E_I	0 86	142	220	122	166	9 3	65	17 9	92	45
	E_{II}	1 31	181	230	130	177	12 1	67	14 6	108	46
67	R	0 21	93	177	104	132	6 1	66	21 6	34	38
	E_I	0 72	146	200	107	142	8 9	61	16 0	81	39
	E_{II}	1 06	186	227	116	156	10 8	58	14 4	98	40
68	R	0 18	94	176	83	118	5 4	57	21 9	33	36
	R^*	0 18	69	172	80	112	4 4	64	25 5	42	38
	E	0 75	168	240	103	160	8 2	49	19 5	92	42
	E^*	0 75	170	233	102	150	7 6	45	19 7	99	42
						Hypertensive women Stage 2					
69	R	0 22	77	171	105	127	4 9	64	25 9	*46*	*37*
	E_I	0 91	138	205	116	152	11 2	81	13 6	81	39
	E_{II}	*1 17*	169	193	113	144	12 8	76	11 3	*91*	40
70	R	0 25	79	224	115	149	5 6	71	26 6	45	31
	E	0 85	152	273	145	203	10 0	66	20 3	85	33

Table II (continued)

Pat	State	V_{O_2}	HR	$P_{S_{BA}}$	$P_{D_{BA}}$	$\bar{P}_{BA}$	Q	SV	SVR	$(a-v)_{O_2}$	Hct
71	R	0 24	89	216	125	157	4 9	55	32 0	48	37
	E	*1 20*	*169*	*250*	126	174	12 0	71	14 5	*100*	42
72	R	0 23	79	166	108	131	5 7	72	23 0	41	40
	E	0 88	*114*	*190*	115	148	8 6	75	17 3	102	43
73	R	0 25	79	185	103	133	5 0	63	26 6	49	29
	E_I	0 92	*124*	*219*	*104*	*150*	9 8	79	15 3	93	32
	E_{II}	*1 28*	153	*233*	102	150	12 9	84	11 6	*99*	32
74	R	0 25	78	184	*99*	*138*	5 7	73	23 8	44	40
	R	0 28	82	183	103	135	5 4	66	25 0	53	40
	E_I	0 93	137	217	121	159	9 1	66	17 5	102	41
	E_{II}	1 11	183	234	146	167	10 6	*58*	*15 8*	*105*	*41*
75	R	0 [illegible]3	83	161	88	114	6 5	78	17 5	36	36
	E_I	0 80	141	194	103	142	10 3	73	13 8	78	40
	E_{II}	*1 06*	166	222	111	152	11 5	69	13 2	*92*	41
76	R	0 21	97	194	115	145	3 9	40	37 2	54	38
	E	0 [illegible]0	142	238	125	169	*7 5*	*53*	*22 6*	*1[illegible]1*	40
77	R	0 [illegible]0	83	180	111	140	4 9	59	28 6	42	38
	R	0 19	77	182	113	143	4 5	58	31 8	42	38
	E	1 15	167	252	129	181	12 6	75	14 4	92	44
78	R	0 23	77	201	117	150	5 2	68	28 9	43	40
	E_I	0 [illegible]8	109	223	123	171	7 6	70	22 5	102	42
	E_{II}	1 14	157	259	128	180	10 2	65	17 7	111	43
79	R	0 18	83	246	111	160	3 5	42	45 7	50	39
	E	*0 73*	*138*	273	116	181	6 3	46	28 7	*116*	42
80	R	0 13	68	171	75	117	6 1	90	19 2	22	35
	E_I	0 83	*136*	*194*	85	131	9 9	73	13 2	84	37
	E_{II}	1 34	156	222	96	151	13 3	85	11 4	101	38
81	R	0 [illegible]7	*81*	153	88	114	6 2	77	18 4	43	36
	E_I	1 04	152	191	95	132	11 4	75	11 6	91	39
	E_{II}	1 41	174	195	97	135	13 2	*76*	*10 2*	107	40
82	R	0 19	74	161	92	119	5 5	74	21 6	35	34
	E	0 95	159	232	112	163	12 3	77	13 3	77	39
	E	0 89	151	219	109	150	11 8	78	12 7	75	37
83	R	0 [illegible]0	9	219	107	148	4 1	52	38 1	*49*	38
	R	0 [illegible]	86	199	106	148	4 3	50	34 4	*50*	38
	E	0 85	148	254	121	184	8 7	55	21 2	98	40
84	R	*0 32*	*109*	304	142	207	5 8	53	35 7	65	41
	E	1 08	165	295	135	198	9 6	58	20 6	113	44
	E	*1 01*	161	263	115	185	8 4	52	19 7	*1[illegible]3*	42
85	R	0 3[illegible]	90	195	102	140	[illegible] 1	57	27	62	38
	E_I	1 03	140	224	107	151	[illegible] 9	56	19 1	130	42
	E_{II}	1 48	*162*	249	*102*	154	10 4	64	14 8	142	42

Table II (continued)

Pat	State	$\dot V_{O_2}$	HR	$P_{S_{BA}}$	$P_{D_{BA}}$	$\bar P_{BA}$	Q	SV	SVR	$(a-v)_{O_2}$	Hct
					Hypertensive women Stage 3						
86	R	0.21	76	179	96	126	7.4	97	17.0	28	32
	E_I	0.71	108	210	99	145	10.2	94	14.2	70	33
	E_{II}	1.06	160	242	109	155	14.3	89	10.8	74	34
87	R	0.30	84	154	97	118	5.3	63	22.3	57	39
	E_I	0.79	137	177	109	136	7.8	50	17.4	101	40
	E_{II}	1.26	180	178	106	134	9.7	54	13.8	129	42
88	R'	0.25	74	141	82	105	4.8	65	21.9	52	41
	R''	0.25	68	134	77	100	4.9	72	20.4	51	41
	E	1.05	131	181	90	124	9.2	70	13.5	114	45
89	R	0.27	78	171	91	118	5.3	68	22.3	51	32
	E	0.78	157	222	106	145	9.8	62	14.8	79	36
90	R	0.23	72	195	115	150	5.8	81	25.9	40	38
	E	1.21	152	255	138	190	11.9	78	16.0	102	42
91	R	0.19	71	180	91	127	3.5	49	36.3	54	36
	R''	0.19	69	183	92	129	3.5	51	36.9	36	36
	E	0.85	125	197	95	143	7.7	62	18.6	110	40
92	R	0.23	84	144	76	100	5.5	66	18.2	42	34
	R''	0.21	82	141	78	104	5.5	67	18.9	39	34
	E	1.05	170	206	90	128	11.5	68	11.1	92	40
93	R	0.22	85	166	103	128	4.0	47	32.0	56	35
	R''	0.21	79	174	107	131	3.9	49	33.6	53	35
	E	0.76	134	224	109	156	8.1	60	19.3	94	38
94	R	0.24	73	264	105	159	4.3	59	37.0	57	35
	R''	0.25	73	272	110	163	4.5	62	36.2	54	36
	E	0.85	129	297	105	175	7.5	58	23.3	114	38
	E''	0.81	123	264	102	160	7.8	63	20.5	104	38
95	R	0.19	67	168	95	117	5.9	88	19.8	33	36
	E	1.16	162	263	115	171	13.9	86	12.3	84	40
96	R	0.24	81	214	103	147	4.1	51	35.9	58	40
	E	0.76	123	257	118	179	6.7	54	26.7	114	44
97	R	0.23	77	160	97	119	3.8	49	31.3	61	46
	E	0.85	158	185	120	141	7.5	47	18.8	113	48
98	R	0.27	76	214	99	139	4.7	62	29.6	57	39
	E	0.90	128	229	104	154	8.0	63	19.3	113	42
99	R	0.23	79	250	128	184	5.0	63	36.8	46	38
	E	0.86	142	331	143	225	8.5	60	26.5	101	42

Symbols R = determination at rest R and R' indicate two consecutive determinations at rest
E = determination during exercise E and E' indicate determinations during two consecutive periods of exercise at same level
$\dot{V}_{O_2}$ = oxygen consumption in liters per min.
HR = heart rate in beats per min
$P_{S_{BA}}$ = systolic brachial artery pressure in mm Hg
$P_{D_{BA}}$ = diastolic brachial artery pressure in mm Hg
$\bar{P}_{BA}$ = mean brachial artery pressure in mm Hg
Q = cardiac output in liters per min.
SV = stroke volume in ml
SVR = systemic vascular resistance in arbitrary units
$(a-\bar{v})_{O_2}$ = arteriovenous oxygen difference in ml per liter
Hct = hematocrit in per cent

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